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(1) Thorn, G.W.; Quinby, J.T., and Marshall, C., Jr., Ann. Int. Med. 18:913 (June) 1943.
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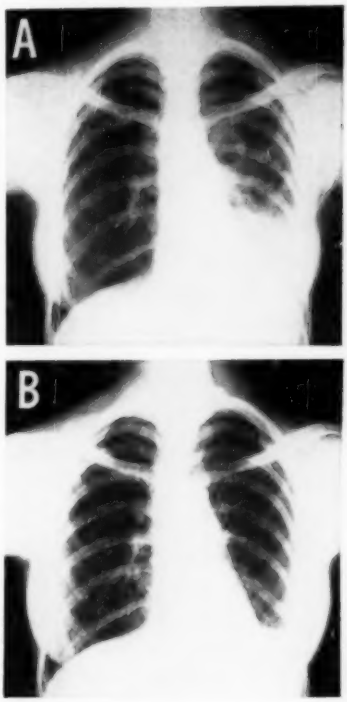

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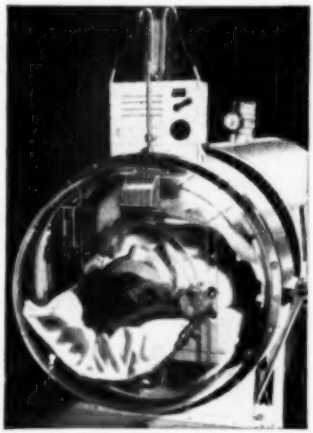

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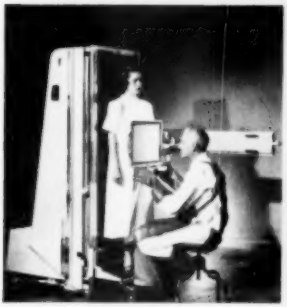

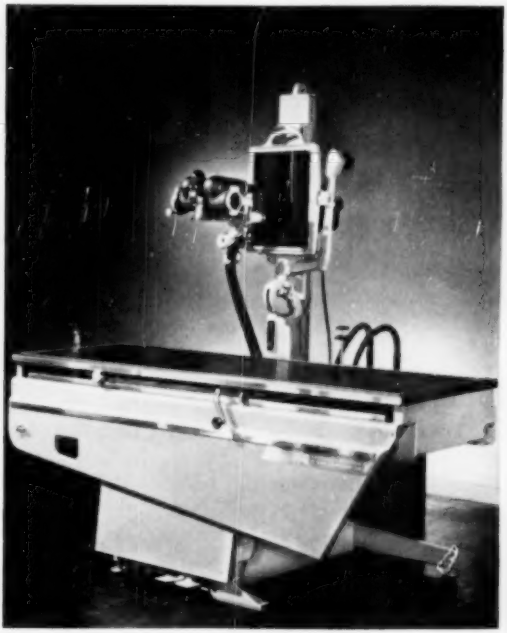

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EFFECTS OF CORTISONE ON THE DEVELOPMENT OF TUBERCULOUS LESIONS IN GUINEA PIGS AND ON THEIR MODIFICATION BY STREPTOMYCIN THERAPY[1,2]

DAVID M. SPAIN AND NORMAN MOLOMUT

(Received for publication May 4, 1950)

INTRODUCTION

Administration of cortisone has been shown to inhibit the formation of granulation tissues (1, 2), to depress macrophage activity (3), to deplete lymphoid tissue (4), and to reduce the function of the reticulo-endothelial system as indicated by reduction in spleen size (5, 6). These factors are of prime importance in the total animal response to experimental tuberculous infection. For this reason the present investigation was undertaken to assess the effects of cortisone on a developing tuberculous infection. The animal responses to the infection were studied under conditions of relatively rapid development as compared with animals in which the course of tuberculosis was partially contained by concurrent streptomycin therapy. In view of the limited supply of cortisone available to us, the experiments were devised to be of relatively short duration and to utilize a limited number of animals. Results of our previous studies (2, 3, 5) of the effects of cortisone on the factors under investigation led us to assume that a statistical evaluation would not be essential since the effects were marked as compared with untreated animals.

Materials and Methods

Forty female guinea pigs weighing 325 to 375 gm. were observed under controlled conditions for normalcy. The animals were then tuberculin tested, and divided into groups of ten. The infecting organism employed was *M. tuberculosis* (H37Rv),[3] grown on Petrik's modification of Löwenstein's medium. A previously grown culture was weighed and emulsified under aseptic conditions so that the infecting dose per animal was equivalent to 0.2 mg. of dry weight of bacilli. Injections were made subcutaneously over the sternum. This infecting site has the advantage of permitting one to follow the course of the local disease in each animal during the experiment (7). Fourteen days after infection each

[1] From the Department of Laboratories and Research, Westchester County, Valhalla, N. Y., and Waldemar Medical Research Foundation, Brooklyn, N. Y.

[2] Supported in part by Helen and Max Borgenicht Foundation.

[3] Obtained from Mr. W. Steenken, Jr., National Culture Bank, Trudeau Foundation, Saranac Lake, N. Y.

animal was skin tested with tuberculin (0.1 ml. of 5 per cent OT) and all animals were found to have positive reactions. (Prior to this time, 4 animals died and on autopsy exhibited signs of pneumonia.) Two days later, treatment was started. The material administered to the various groups was as follows: Group 1, saline; Group 2, cortisone acetate, 5 mg. daily; Group 3, streptomycin hydrochloride base, 10 mg. daily; and Group 4, cortisone acetate, 5 mg., and streptomycin hydrochloride base, 10 mg., daily.

In each group above, the given agent was administered in a volume of 1.0 ml. and was injected subcutaneously in the dorsum each day for twenty-eight consecutive days. Daily observation of the infection site was made. The size, degree of localization, and

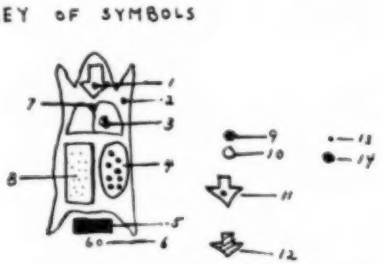

FIG. 1. Schematic representation showing key of symbols indicating extent of tuberculous lesions of guinea pigs seen at necropsy (modified by authors from Feldman, W. H., and Hinshaw, H. C.: Am. Rev. Tubere., 1945, *51*, 582).

Key:

1. Lesion over sternum at site of inoculation
2. Involvement of axillary lymph nodes
3. Involvement of lungs
4. Nodular tuberculosis of spleen
5. Animal died
6. Days of infection
7. Involvement of mediastinal lymph nodes
8. Miliary tubercles of liver
9. Caseation necrosis
10. Granulomatous lesion with no caseation
11. Localized lesion at inoculation site
12. Diffuse lesion at inoculation site
13. Small lesion
14. Large lesion

time of ulceration were noted. Tuberculin tests were repeated at the end of treatment and one-half of the animals in each group were sacrificed. The remaining animals were continued under observation without treatment for an additional fourteen days, at which time tuberculin tests were performed and the animals sacrificed as above. Each animal was weighed prior to sacrifice. Complete autopsies were performed with particular attention to the site of inoculation, axillary lymph nodes, mediastinal lymph nodes, spleen, liver, and lungs. Gross and microscopic observations were recorded, employing the schema of Feldman and Hinshaw (8). For the purpose of this experiment, the original method of recording was modified so that the degree of caseation, size, and localization of the lesion at the site of infection are given (figure 1). Further, in our method of recording the size, the degree of caseation and number of lymph nodes involved are also given.

RESULTS

The comparative findings among the four groups of animals treated as described are illustrated in figures 2 and 3.

Lesions at the site of infection: The nodules at the site of infection appeared earliest in the controls treated with saline. This observation is probably due to the fact that, although significant local lesions developed in the animals treated

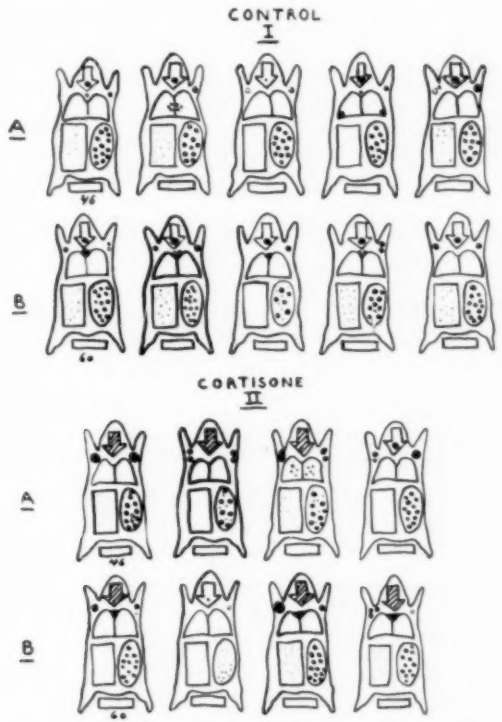

FIG. 2. Schematic representation of degree and type of involvement of controls (Group I) and animals treated with cortisone (Group 2). (A) represents animals sacrificed immediately after cessation of therapy; (B) represents animals sacrificed 14 days after cessation of therapy.

with cortisone, the lesions were diffuse and difficult to differentiate by palpation. The average area of spread of this site was 0.5 cm. in the control animals, and the lesions were discrete and well-encapsulated in fibrous tissue (figure 4). In 6 of the animals treated with cortisone, the site was diffusely nodular, covering an irregular area 1 cm. or greater in diameter. These lesions were incompletely encapsulated with scant granulation tissue and with many areas devoid of granulation tissue (figure 5). In both the controls (Group 1) and the animals treated

with cortisone (Group 2), caseation was observed in approximately the same degree. Although the animals treated with streptomycin (Group 3) exhibited markedly less involvement, they showed the same type of discrete, well-encapsulated nodule as did the controls (Group 1). In contrast, the animals treated with both cortisone and streptomycin (Group 4) at no time exhibited palpable nodules during the entire treatment period. One week after cessation of treat-

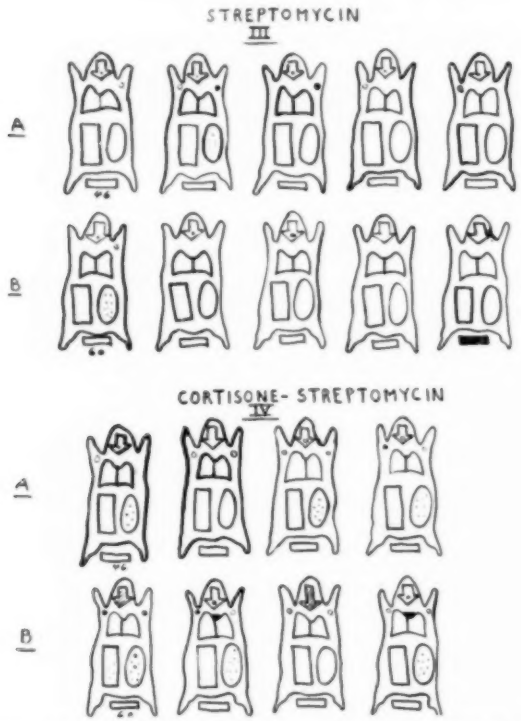

FIG. 3. Schematic representation of degree and type of involvement of animals treated with streptomycin (Group 3) and animals treated with both cortisone and streptomycin (Group 4). (A) represents animals sacrificed immediately after cessation of therapy; (B) represents animals sacrificed 14 days after cessation of therapy.

ment, among the animals not sacrificed, in 3, diffusely nodular lesions appeared and a localized lesion in one at the end of the fifty-sixth day after infection. These latter nodules, despite their late appearance, surpassed in size and extent the lesions of the streptomycin group and were more diffuse than those in the control group. This late but greater involvement occurred despite the concurrent streptomycin therapy.

Observations on extent of tuberculous involvement: All animals were sacrificed too

soon after infection to permit development of any significant pulmonary involvement. The involvement was graded on the basis of extent, size, and numbers of nodules and degree of caseation occurring in the axillary and mediastinal lymph nodes, liver, and spleen. The control animals (Group 1) exhibited moderate to

TABLE 1

Observations on Lesions at the Site of Infection

TREATMENT	NUMBER OF ANIMALS	TIME OF DEVELOPMENT OF PALPABLE NODULE, DAYS AFTER INFECTION	NUMBER OF ANIMALS	CHARACTER OF NODULE			
				Localized	Diffuse	None	Ulceration
Saline	10	20 to 24	9	10	0	0	8
Cortisone, 5 mg. daily	8	26 to 30	7	2	6	0	0
Streptomycin, 10 mg. daily	10	30 to 32	8	8	0	2	0
Cortisone, 5 mg. daily; streptomycin, 10 mg. daily	8	54 to 56	4*	3	4	1	0

* These 4 animals were kept alive after treatment was ceased. The 4 animals sacrificed at termination of treatment did not have palpable nodules prior to sacrifice.

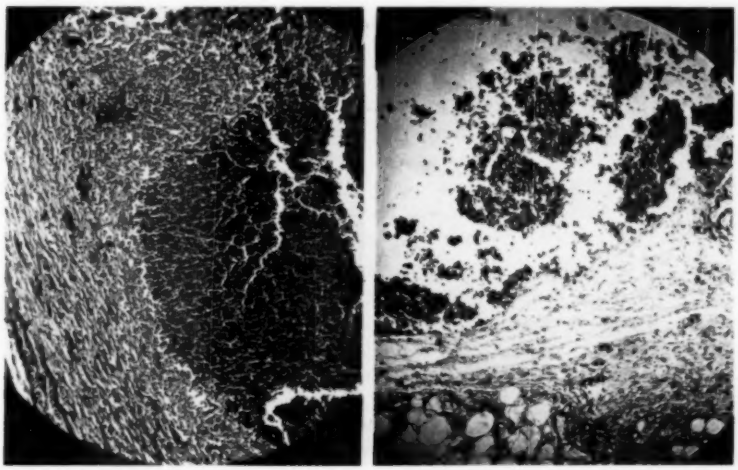

FIG. 4 (Left). Photomicrograph showing well-encapsulated nodule at site of inoculation, with considerable fibrous tissue at edge of lesion. (Control animal)

FIG. 5 (Right). Photomicrograph showing poorly encapsulated lesion at site of inoculation. There is scant granulation tissue at edge of lesion. (Animal treated with cortisone)

marked involvement of the spleen in every instance, minimal lesions of the liver, and small to moderate-sized lymph nodes with varying degrees of caseation. The members of this group, sacrificed fourteen days after cessation of saline injections, showed, in addition, moderate involvement of the mediastinal lymph

nodes in 4 of 5 animals. In 3 of these latter, caseous foci were found. The animals treated with cortisone (Group 2) showed involvement of the spleen and liver equivalent to that of the controls. The axillary lymph nodes exhibited notably greater involvement, in that more nodes were implicated, the nodes were larger, and more caseous necrosis was seen. Three of the animals sacrificed fourteen days after cessation of cortisone injections had massive caseous mediastinal lymph nodes. These findings were confirmed by histologic examination. The animals treated with streptomycin (Group 3) revealed minimal involvement of the spleen in only 2, and there were no liver lesions. The lymph nodes were small in 6 animals and caseation was present in 2. No mediastinal lymph nodes were noted in any of this group. The animals treated with cortisone and streptomycin (Group 4) showed only minimal involvement of the spleen as did the animals in Group 3, but lesions were present in more animals of this group, i.e., in 6 of the 8 animals lesions were noted. One animal had minimal lesions of the liver. All 8 animals showed greater involvement of the axillary lymph nodes. In 2 of the 4 animals sacrificed fourteen days after cessation of treatment, there were moderately enlarged mediastinal lymph nodes with caseous necrosis as compared with the streptomycin controls (Group 3) in which this finding was absent.

DISCUSSION

The tuberculous lesion is a dynamic process which may at any one time exhibit signs of spread, containment, resolution, necrosis, and organization. The main direction of a tuberculous lesion at any one time (towards healing or towards further destruction and activity) depends upon the interplay of many factors. Those forces acting to contain the tuberculosis are usually grouped under the general term of resistance. Many of the factors of resistance are known and many remain unknown. None can be measured accurately, but one may safely include such forces as the physiologic background of the individual, the nutritional state, racial background, the ability to form granulation tissue, macrophage activity, and immune response. It has been demonstrated that cortisone produces many biological effects, among which are inhibition of formation of granulation tissue, interference with macrophage activity, and depletion of the lymphocyte reserves of the body. All of these forces are generally considered necessary for the resistance to progression of the tuberculous lesion. It would seem, therefore, that under ordinary conditions an excess of cortisone in the body would exert a deleterious effect on the body's ability to handle a tuberculous infection. This indeed was the case in the limited type of experiment on guinea pigs described in this report. It would seem that until further data on cortisone are available there is no place for its use in the treatment of human tuberculosis. It should also be borne in mind that cortisone therapy directed at other conditions such as rheumatoid arthritis, rheumatic fever, and the group of collagen diseases might cause the flare-up of previously unrecognized, latent tuberculous lesions in those individuals subjected to this treatment.

Because of the effects of cortisone on granulation tissue, it has been thought by some that it exhibits a fibrolytic action. It was believed, therefore, that, if

cortisone were to be administered concurrently with an antituberculous agent such as streptomycin, it might allow the antituberculous agent to attack tubercle bacilli ordinarily inaccessible. In our opinion, cortisone does not exert a fibrolytic action. It does not appear to have any demonstrable action on granulation tissue already formed (2). For this reason the above concept does not appear tenable at present. In the experiments described in this report the tuberculous lesions in the group of animals treated both with cortisone and streptomycin did not show the same degree of localization and healing as in the group treated only with streptomycin.

It was noted in these experiments that the last tuberculin reactions in the animals treated with cortisone were unequivocally more edematous than in those of the other groups. It is possible that the explanation for this lies in the demonstrated anti-hyaluronidase activity of cortisone (9). With increased anti-hyaluronidase activity the edema fluid may not have been removed as rapidly as in the other animals. It is conceivable that inhibition of granulation tissue may also in some way be related to the same effect of cortisone on anti-hyaluronidase activity.

SUMMARY

Four groups of guinea pigs experimentally infected with tuberculosis were treated respectively with saline solution, cortisone, streptomycin, and cortisone combined with streptomycin. The lesions in those animals receiving cortisone appeared to be more extensive, more widely distributed, and less well localized than in the others.

SUMARIO

Efecto de la Cortisona sobre la Aparición de Lesiones Tuberculosas en los Cobayos y Modificación de las Mismas por la Estreptomicina

Cuatro grupos de cobayos infectados experimentalmente con tuberculosis fueron tratados, respectivamente, con solución salina, cortisona, estreptomicina y cortisona combinada con estreptomicina. Las lesiones observadas en los animales que reibieron cortisona parecieron ser más extensas, más esparcidas y menos bien localizadas.

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THE EFFECT OF NEOMYCIN ON TUBERCULOSIS IN GUINEA PIGS INFECTED WITH STREPTOMYCIN-RESISTANT TUBERCLE BACILLI[1]

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INTRODUCTION

The administration of neomycin has been reported to prolong the survival time of mice infected with streptomycin-sensitive tubercle bacilli (1, 2) and to cause regression and healing of tuberculous lesions in guinea pigs in which the disease, due to streptomycin-sensitive tubercle bacilli, had been established before treatment was started (3). It has been found that the growth of streptomycin-resistant tubercle bacilli is inhibited *in vitro* by neomycin (4, 5). The following report is concerned with an experiment in which it was demonstrated that the administration of neomycin had a marked therapeutic effect on experimental tuberculosis in guinea pigs infected with streptomycin-resistant tubercle bacilli.

Methods

Thirty-two male guinea pigs, weighing approximately 750 gm. each, were inoculated subcutaneously over the sternum with 0.1 mg. (moist weight) of a streptomycin-resistant strain of human-type tubercle bacillus.[2] The culture was resistant *in vitro* to more than 1,000 γ of streptomycin per ml. of egg-yolk agar. On the twenty-first day of infection 6 animals (pretreatment controls) were killed and were found to have grossly visible lesions of tuberculosis in the lungs, liver, and spleen, as shown in figure 1. It is presumed that the remaining 26 animals had as extensive tuberculous involvement of the usual organs of predilection as was seen in the pretreatment control animals.

On the twenty-first day of infection the 26 remaining animals were divided into three groups as follows: 10 animals which served as untreated controls, 6 animals which were started on treatment with 6 mg. of streptomycin once daily injected into the axillary space, and 10 animals which were started on treatment with neomycin.[3] The streptomycin was administered to one group to obtain evidence that the infecting microorganism was resistant to streptomycin *in vivo*. No data were available concerning the toxicity of neomycin for guinea pigs. It was arbitrarily decided to start with 2,000 units of neomycin given in the axillary space twice daily. The daily dose of neomycin was subsequently increased on several occasions when it was found that the drug was being tolerated as determined by the maintenance of body weight. Accordingly, the complete dosage schedule was as follows: 2,000 units twice daily for six days; 4,000 units twice daily for eighteen days; 6,000 units twice daily for twenty-three days; and finally, 8,000 units twice daily for thirty days.

The experiment was terminated after the seventy-seventh day of treatment. All of the surviving animals were then killed, and a record was made of the extent of tuberculosis

[1] From the Division of Experimental Medicine, Mayo Foundation, Rochester, Minnesota.

[2] This culture was isolated from a patient after ninety days of treatment with 2 to 3 gm. of streptomycin daily.

[3] The neomycin used in this experiment was furnished through the courtesy of Dr. R. J. Hickey, Commercial Solvents Corporation, Terre Haute, Indiana.

seen at necropsy. Portions of the site of inoculation, the axillary lymph nodes, lungs, tracheobronchial lymph nodes, spleen, liver, and one kidney were preserved for histopathologic examination.

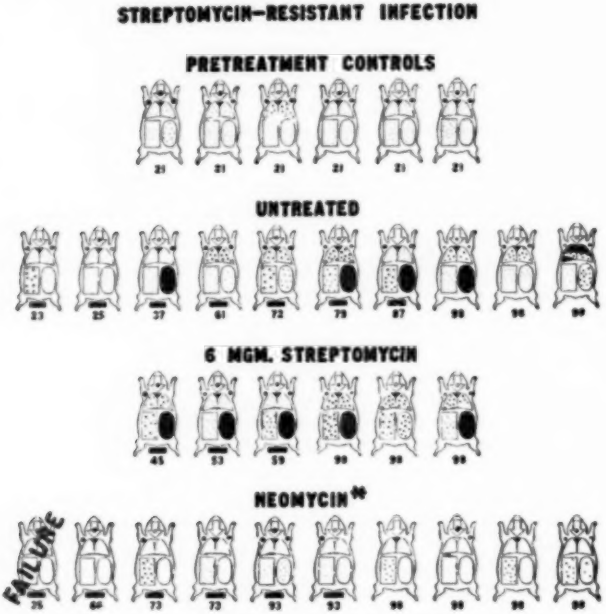

FIG. 1. Schematic presentation of the extent of tuberculosis seen at necropsy. The rectangle and oval represent the liver and spleen, respectively. The large dot or circle in the arrow represents an abscess or ulcer at the site of inoculation. Miliary and nodular lesions are indicated by small and large dots. Diffuse involvement of an organ is indicated by complete blackening. The numerals show the number of days of infection and the black bar indicates that the animal died before the experiment was completed. The animal marked "failure" was not adequately examined owing to post-mortem changes.

* Dosage of neomycin: 2,000 units twice daily for six days, 4,000 units twice daily for eighteen days, 6,000 units twice daily for twenty-three days, and finally, 8,000 units twice daily for thirty days for a total of seventy-seven days of treatment.

RESULTS

Drug tolerance: Unfortunately, losses which could not be ascribed to tuberculosis occurred in the groups of treated animals as well as in the untreated controls.[4] The animals which died appeared to be ill for only a few days, during which time they rapidly lost weight. This adversely affected the average weights for

[4] The cause of these deaths was not determined. In several animals examined immediately after death, the lungs were congested. Blood agar cultures of the lungs revealed nothing of significance.

each group. In spite of this complication, the surviving animals continued to gain weight slightly even when the dose of neomycin was increased to 8,000 units twice daily. There was no evidence that the administration of neomycin had any deleterious effect on the growth of the animals, nor were there any other physical signs of toxic effects of the drug.

Necropsy findings: As shown in figure 1, the widespread tuberculous disease seen at necropsy in the animals treated with streptomycin presented definite evidence that the infecting strain of tubercle bacilli was resistant to streptomycin. The extent of the tuberculous lesions observed in the animals treated with neomycin was strikingly less than that seen in the untreated animals and in those given streptomycin. Furthermore, the degree of involvement was obviously much less than had been recorded for the pretreatment controls, as shown in figure 1. Only one of the animals given neomycin had pulmonary lesions discernible at necropsy and these were minimal. This is in contrast to the findings in the other animals, all of which, with one exception, had visible lesions in the lungs, as indicated in figure 1. In addition, only 3 animals treated with neomycin had lesions in the spleen, whereas every other animal, including those killed after twenty-one days of infection, had extensive involvement of this organ as seen at necropsy. Seven of the animals given neomycin had grossly visible lesions of the liver although to a lesser extent than in the untreated controls, and 7 had residual lesions either at the site of inoculation or in the axillary lymph nodes.

Of particular interest were the results observed in the animals that died from causes other than tuberculosis before completion of the treatment period. The animals which died on the sixty-sixth, seventy-third, and ninety-third days of infection received treatment for forty-five, fifty-two, and seventy-two days, respectively, and each was found to have less disease than was seen in the untreated animals that died before the experiment was completed.[5]

Histopathologic examination: Microscopic examination provided additional evidence that the administration of neomycin effected retardation and healing of the disease process. In contrast to the progressive lesions characterized by widespread destruction of tissue in the untreated animals (figure 2a) and in those given streptomycin, the signs of regression and healing, such as fibrosis and calcification, were predominant in the lungs and spleens of the animals treated with neomycin (figure 2b). There were, however, small active foci in the livers of 6 animals treated with neomycin, but the extent of involvement was less than that in the untreated animals. Furthermore, there were persistent active foci at the site of inoculation or in the contiguous lymph nodes in 7 animals.

An average index of infection based on histopathologic characteristics (6) was determined for each group. By this method, actively progressing disease in each organ shown in table 1 is given a value ranging from 10 to 35 depending on the extent of involvement. Inactive and nonprogressive lesions with fibrosis or calcification are given values of 1 to 3. Referring to table 1, it is seen that, on this

[5] The first animal to die in the group treated with neomycin received treatment for only fourteen days. It could not be adequately examined owing to extensive post mortem changes and was, therefore, considered as a "failure."

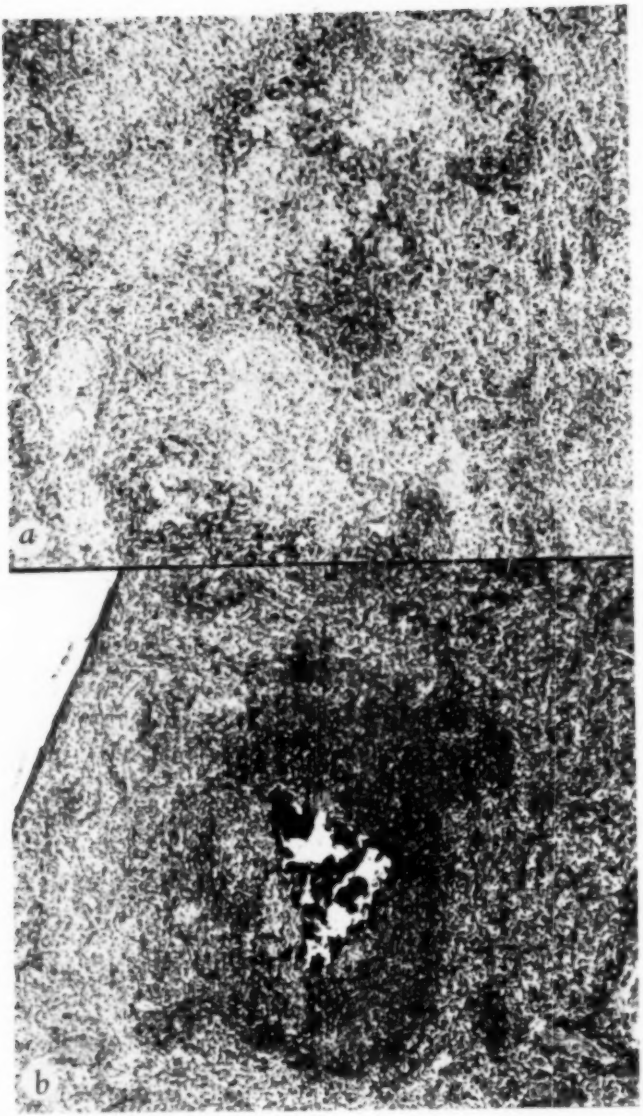

FIG. 2a. Spleen of an untreated guinea pig killed ninety-eight days after infection with 0.1 mg. of a streptomycin-resistant strain of tubercle bacilli. There is extensive progression of the tuberculous process with diffuse destruction of the normal tissue (×64). b. Spleen of a guinea pig treated with neomycin for seventy-seven days. Treatment started twenty-one days after infection with 0.1 mg. of a streptomycin-resistant strain of tubercle bacilli. The only evidence of a previously active process is a calcified region (×64).

basis, the animals treated with streptomycin had as much disease as did the untreated animals. The animals treated with neomycin, however, had less active disease than either of the foregoing and—a fact of particular interest—had less

TABLE 1

Average Severity of Tuberculosis Expressed Numerically Based on Histopathologic Characteristics (6) of Streptomycin-resistant Infection

NUMBER OF ANIMALS	TREATMENT	SPLEEN (MAX.: 35)	LUNGS (MAX.: 30)	LIVER (MAX.: 25)	SITE OF INOCULATION (MAX.: 10)	AVERAGE INDEX OF INFECTION (MAX.: 100)
6	None*	20.0	10.0	15.0	10.0	55.0
10	None	30.0	21.1	22.2	10.0	83.3
6	6 mg. of streptomycin daily	25.0	24.1	25.0	10.0	84.1
9†	Neomycin	5.1	0.0	10.3	8.0	23.4

* Pretreatment control animals killed twenty-one days after infection.

† One of the original 10 animals died after only fourteen days of treatment and is not included in the table.

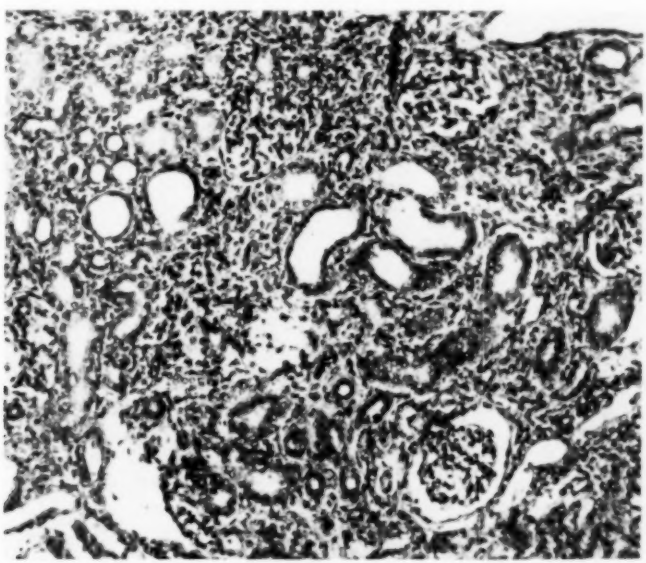

FIG. 3. Section of the cortex of a kidney from a guinea pig treated with neomycin for seventy-seven days. Tubular degeneration and cellular infiltration is present.

disease than had been recorded for the pretreatment control animals. The data indicate that there was not only inhibition of the morbid process but an actual regression as the result of the administration of neomycin.

Renal lesions: In each of the animals treated with neomycin, the kidneys were found to have discrete lesions of the cortex characterized by tubular degeneration and cellular infiltration, as depicted in figure 3. Structures between these altered areas, including glomeruli, appeared to be normal. Approximately 10 per cent of the area of the renal cortex examined appeared to be involved. The lesions were identical with those previously reported to have occurred in guinea pigs treated with neomycin (3).

COMMENT

Using comparable doses, the therapeutic effect of neomycin observed in this experiment in which the infecting microorganism was resistant to streptomycin was similar in every respect to that previously reported for experimental tuberculosis in guinea pigs due to streptomycin-sensitive tubercle bacilli (3). This finding fulfills one of the requirements of a new antimicrobial agent, i.e., that it be active against microorganisms "which are not sensitive to or which have become resistant to presently accepted chemotherapeutic agents" (5). The occurrence of streptomycin-resistant tubercle bacilli in patients being treated with streptomycin is one of the important disadvantages of its use. The finding of chemotherapeutic agents which may be effective in clinical tuberculosis due to streptomycin-resistant tubercle bacilli is obviously of primary importance.

In this experiment it was considered desirable to use large doses of neomycin in order to detect any potential beneficial effect on the experimental infection. Having established that this agent has marked therapeutic properties in experimental tuberculosis in the amounts used, further studies will be required to learn the optimal therapeutic dose and the optimal frequency of administration for guinea pigs.

Whether the renal lesions seen in the animals treated with neomycin are due to the large doses used and whether serious damage to the kidneys may be averted by administering smaller amounts of the drug, given either alone or in combination with some other antituberculosis agents, are problems for future investigation. There is an inviting possibility of combining the use of neomycin, even in low doses to preclude serious renal damage, with the use of *p*-aminosalicylic acid or with 4-acetylaminothiosemicarbazone, or both. These latter agents have been found to be therapeutically active against experimental tuberculosis in guinea pigs infected with streptomycin-resistant tubercle bacilli (7).

SUMMARY AND CONCLUSIONS

Thirty-two guinea pigs were infected subcutaneously with streptomycin-resistant tubercle bacilli. Twenty-one days later 6 were killed and found to have grossly visible lesions of tuberculosis. The remaining animals were then divided into three groups consisting, respectively, of 10 untreated control animals, 6 treated with 6 mg. of streptomycin daily, and 10 treated with neomycin. Treatment was started on the twenty-first day of infection. The dosage schedule for neomycin was as follows: 2,000 units twice daily for six days, 4,000 units twice daily for eighteen days, 6,000 units twice daily for twenty-three days, and 8,000

units twice daily for thirty days. The experiment was ended after seventy-seven days of treatment. In contrast to the widespread destructive lesions seen in the untreated animals and in those treated with streptomycin, there were few grossly visible lesions in the animals treated with neomycin, and histologically the indications of repair and healing such as fibrosis and calcification were predominant. Lesions of the renal cortex characterized by tubular destruction and cellular infiltration were seen in the kidneys of all of the animals treated with neomycin. This demonstration of the therapeutic effect of neomycin in guinea pigs infected with streptomycin-resistant tubercle bacilli warrants further investigation to determine optimal dose, optimal frequency of administration, and its effect when used in combination with other antituberculosis agents. Studies to determine the causes of the renal damage and methods of averting it are of first importance.

SUMARIO Y CONCLUSIONES

El Efecto de la Neomicina sobre la Tuberculosis en los Cobayos Infectados con Bacilos Tuberculosos Estreptomicinorresistentes

Treinta y dos cobayos fueron infectados subcutáneamente con bacilos tuberculosos estreptomicinorresistentes. Al matar a 6 veintiún días después, descubriéronse en ellos lesiones macroscópicas de tuberculosis. A los demás animales se les dividió entonces en tres grupos, compuestos, respectivamente, de: 10 testigos no tratados, 6 tratados con 6 mg. diarios de estreptomicina y 10 tratados con neomicina. El tratamiento fué iniciado al vigésimoprimer día de la infección. El esquema posológico para la neomicina fué el siguiente: 2,000 unidades dos veces diarias durante seis días, 4,000 unidades dos veces diarias durante dieciocho días, 6,000 unidades dos veces diarias durante veintitrés días y 8,000 unidades dos veces diarias durante treinta días. El experimento terminó al cabo de setenta y siete días de tratamiento. En contraposición a las diseminadas lesiones destructoras observadas en los animales no tratados y en los tratados con estreptomicina, había pocas lesiones macroscópicas en los tratados con neomicina, e histológicamente predominaban los indicios de regeneración y cicatrización, tales como fibrosis y calcificación. En los riñones de todos los animales tratados con neomicina, notáronse lesiones de la corteza renal caracterizadas por destrucción tubular e infiltración celular. Esta demostración del efecto terapéutico de la neomicina en los cobayos infectados con bacilos tuberculosos estreptomicinorresistentes justifica nuevas investigaciones encaminadas a determinar la dosis óptima, la frecuencia óptima de administración y el efecto de la droga cuando se usa en combinación con otros agentes antituberculosos. Los estudios dirigidos a determinar las causas de las lesiones renales y los medios de evitarlas revisten importancia primordial.

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ANGIOCARDIOGRAPHY IN ARTIFICIAL PNEUMOTHORAX[1,2]

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INTRODUCTION

Heretofore, visualization studies of pulmonary circulation have been carried out on autopsy material with intravascular injections of opaque material. Pinner (1) questioned the reliability of these studies, indicating that uncontrollable agonal and post-mortem vascular changes may occur. Angiocardiography as described by Robb and Steinberg in 1938 (2) affords a practical method of roentgenographic visualization of the pulmonary artery and its branches in the living patient. In 1931, Moniz, Carvalho, and Lima (3) utilized the cardiac catheterization technique of Forssmann and injected sodium iodide to visualize the pulmonary arterial tree. The purpose of this report is to illustrate the changes occurring in the pulmonary circulation in artificial pneumothorax in the living patient as visualized by the technique of angiocardiography.

Method

For the most part, angiocardiography was conducted as originally described (2), using a standard stereo-cassette changer permitting two films per injection. Contrast substance rapidly injected into an antecubital vein passes into the right heart chambers, then to the pulmonary arteries, returning via the pulmonary veins to the left heart chambers, and finally passing into the aorta. Roentgenograms were taken at appropriate intervals for the best visualization of the pulmonary circulation. In some instances the Fairchild automatic roll-film magazine (4) was used enabling roentgen exposures to be made at half-second intervals during the period of opacification. Either Neo-Iopax 75 per cent or Diodrast 70 per cent were used as the contrast substance. As employed, neither substance causes iodism since the iodine is so bound in an organic molecule as to be unavailable to the body (5).

Twenty-three patients with tuberculosis were studied at varying intervals before, during, and after artificial pneumothorax. Of these, 2 had had bilateral pneumothorax. Interpretation of pulmonary vascular changes was made from the comparison of the opacified pulmonary circulation of the collapsed lung with that of the noncollapsed lung, as well as from comparison of serial contrast studies in the same individual. These changes included variations in the caliber, degree and rate of filling, position, and configuration of the pulmonary vessels.

RESULTS

A definite decrease in vascularity of local areas of the lung involved by tuberculosis has been demonstrated angiocardiographically (5) (figures 1A and 2A), and by injection studies in autopsy material (6).

[1] From the Departments of Radiology and Medicine of The New York Hospital—Cornell Medical Center.

[2] This investigation was aided by grants from The New York Heart Association and The Schering Corporation.

In addition to the avascularity at the site of the tuberculous process, there is, following the institution of pneumothorax, a decrease in vascularization of the collapsed lung (7) (figures 1 to 4). This is evidenced by narrowing and diminished filling of vessels and is most marked in the peripheral third of the lung. The greater the degree of collapse, the greater is the diminution in vascularity (figures 2B and 2C). In contrast studies done by multiple exposure technique, there was a

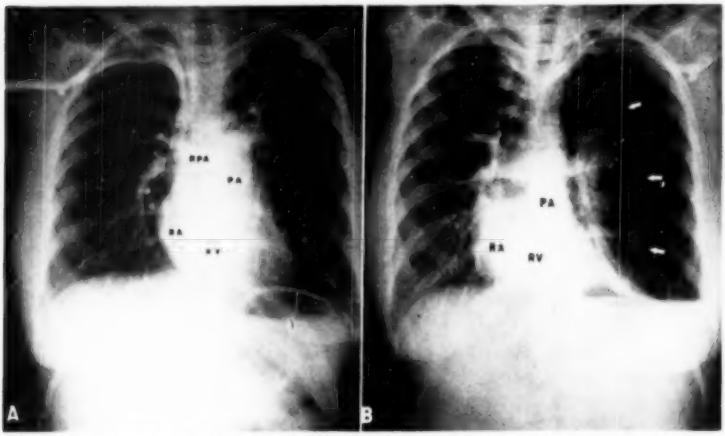

FIG. 1. Visualization study of a 25-year-old white female with moderately advanced tuberculosis of the left upper lobe.

A. Before pneumothorax: Angiocardiogram reveals normally located heart and great vessels. There is evidence of diminished vascularity of the left upper lobe associated with multiple small tuberculous cavities.

B. After three months of effective left pneumothorax (80 per cent), indicated by arrows. Left apical adhesion and small amount of fluid is present. There is marked diminution in the caliber of opacified vessels within the collapsed left lung. An anterior mediastinal hernia is evidenced by the displacement of the superior vena cava to the right. The heart and great vessels have also shifted to the right.

RA —right atrium
RV —right ventricle
PA —pulmonary artery
RPA —right pulmonary artery
SVC —superior vena cava

definite delay in opacification of the pulmonary vessels of the collapsed lung as compared to the normally expanded lung. Crowding, displacement, and torsion of the vessels at the hilum occurred (figure 3). A shift of the heart and great vessels to the side away from the pneumothorax was noted (figures 1 and 2).

In extensive unilateral fibrosis there is retraction of the heart, mediastinum, trachea, and great vessels into the affected side. All of these structures form a homogeneous shadow, the individual parts of which cannot be differentiated on conventional roentgenograms. This may be called "fibrothorax" (8). Angio-

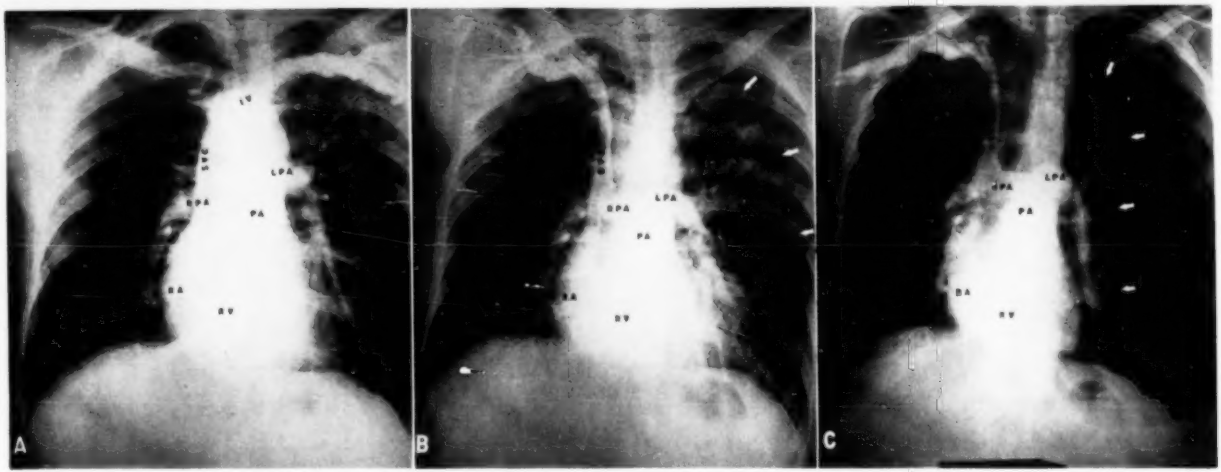

FIG. 2. Visualization study of a 33-year-old Negro male with moderately advanced tuberculosis.

A. Before pneumothorax: As in figure 1A, there is diminished vascularity in association with left upper lobe tuberculous cavitation and infiltration. Mediastinal structures are in the normal position.

B. After one month of left pneumothorax (10 per cent): In addition to the slight shift of the mediastinal structures to the right, the left pulmonary artery has become depressed.

C. After three months of effective left pneumothorax (80 per cent), minimal pleural effusion is present. There is a striking diminution in the vascularity of the collapsed lung. The mediastinal structures have deviated to the right side.

IV —innominate vein
SVC —superior vena cava
RA —right atrium
RV —right ventricle
PA —pulmonary artery
RPA—right pulmonary artery
LPA—left pulmonary artery.

cardiography delineates the great vessels and heart chambers and usually shows rotation and displacement of the structures. Figures 5 and 6 show the changes following right and left re-expanded pneumothorax. In each instance, the vascular supply to the re-expanded lung was found to be markedly diminished. This is in keeping with the pulmonary function studies of Cournand and his associates (9).

It is not within the scope of this paper to discuss the controversial theories by which artificial pneumothorax is held to be beneficial in the healing of pulmonary tuberculosis (1, 10–15). The rapid disappearance of the so-called toxic

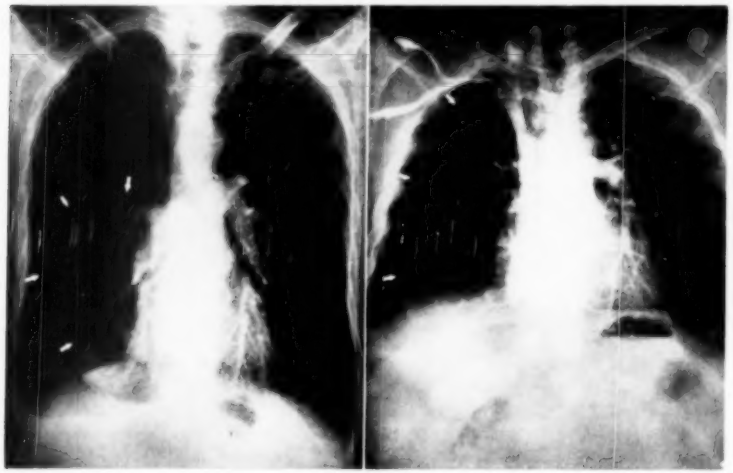

FIG. 3. (Left) Contrast study in a 47-year-old white male with an effective right pneumothorax of two and one-half years' duration. There is remarkable crowding together of the pulmonary vessels on the collapsed right side with diminished opacification as compared to the left side. The ascending branch of the right pulmonary artery is so depressed as to run horizontally into the collapsed right upper lobe. There is also marked torsion of the right pulmonary artery.

FIG. 4. (Right) Visualization study in a 19-year-old white male with a therapeutically effective right pneumothorax (20 per cent) of two and one-half years' duration. There is a general diminution in vascularity of the entire right side, most marked in the periphery, as evidenced by narrowing and lack of filling of pulmonary vessels.

symptoms following institution of artificial pneumothorax in tuberculous patients has been attributed by Carvalho (16) to the diminution of the circulation in the collapsed side and to the diminution in rate of absorption of the bacterial products. These circulatory changes are of particular interest inasmuch as tubercle bacilli have been shown to be strict aerobes requiring large amounts of oxygen for survival and multiplication (18, 19).

Injection studies of autopsy material reveal that the greater the degree of collapse of the lung the greater is the decrease in vascularity (6). Bruns (20)

noted that in the compressed lung the smaller pulmonary blood vessels were collapsed and that only the larger vessels contained much blood. Gardner (21) also found that the greatest evidence of avascularity was present in the peripheral portion of the collapsed lung. The visualization studies herein reported, which were performed on living patients, lead us to conclude that the above autopsy studies actually represent the changes which take place in the pulmonary circulation of the collapsed lung during life rather than the effects of agonal or postmortem changes.

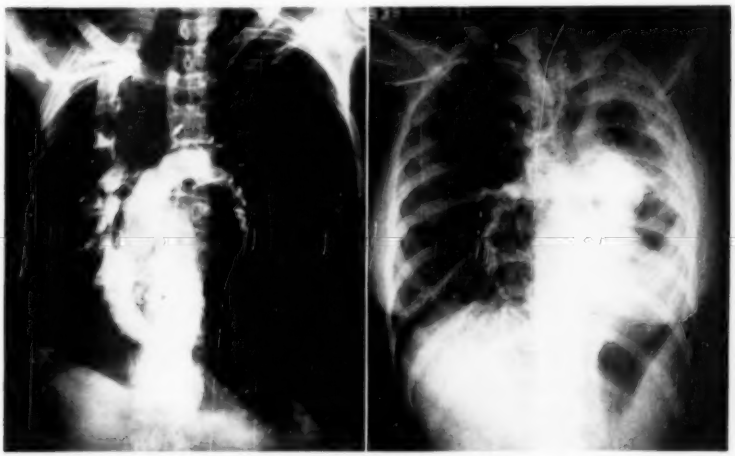

FIG. 5. (Left) Visualization study in a 45-year-old white male with "fibrothorax" ten years after termination of a five-year right pneumothorax. Angiocardiogram shows marked retraction of mediastinal structures to the right with rotation of the heart to the "left anterior oblique" projection. There is diminished vascularity of the entire right lung. Mediastinal herniation of the left lung is demonstrated by the presence of a branch of the left pulmonary artery crossing into the right chest (arrow). The pulmonary vascular supply to the left lung is intact. Its branches are so separated as to suggest emphysema.

FIG. 6. (Right) Angiocardiogram in a 19-year-old Negro female with "fibrothorax" two years after termination of a three-year left pneumothorax. Changes are similar to those noted in figure 5 with retraction of mediastinal structures to the left side and the heart in the "right anterior oblique" projection.

SUMMARY AND CONCLUSIONS

The angiocardiographic findings in the pulmonary circulation of living patients with artificial pneumothorax are illustrated. Angiocardiography usually demonstrates avascularity at the site of moderately advanced or far advanced lesions of pulmonary tuberculosis.

Following artificial pneumothorax the following changes may be noted: (a) decrease in the vascularity of the collapsed lung in proportion to the degree of collapse; (b) delay in rate of the blood flow in the collapsed lung; (c) crowding,

distortion, and displacement of the pulmonary blood vessels in the collapsed lung; (d) varying degrees of shift of the heart, great vessels, and mediastinum to the side opposite the pneumothorax.

In "fibrothorax" following re-expansion of a pneumothorax, angiocardiography serves to delineate the cardiovascular structures. Retraction and torsion of the cardiovascular structures and decreased vascularity to the affected side are demonstrated.

These angiocardiographic findings serve to supplement and confirm previous studies made on post-mortem material. Changes shown by the latter method are apparently not due to agonal processes but represent the vascular status during life.

SUMARIO Y CONCLUSIONES

La Angiocardiografía en el Neumotórax Terapéutico

Preséntanse aquí los hallazgos angiocardiográficos en la circulación pulmonar de enfermos vivos con neumotórax terapéutico. La angiocardiografía suele revelar avascularidad en en el sitio donde radican lesiones moderadamente o muy avanzadas de tuberculosis pulmonar.

A continuación del neumotórax inducido pueden notarse las siguientes alteraciones: (a) disminución de la vascularidad del pulmón aplastado en proporción a la intensidad del colapso; (b) demora en la velocidad del riego sanguíneo en el pulmón aplastado; (c) aglomeración, deformación y desplazamiento de los vasos sanguíneos del pulmón aplastado; (d) desviación en mayor o menor grado del corazón, los grandes vasos y el mediastino al lado opuesto al neumotórax.

En el "fibrotórax" consecutivo a la reexpansión de un neumotórax, la angiocardiografía sirve para delinear los tejidos cardiovasculares, revelando retracción y torsión de los mismos y menor vascularidad del lado afectado.

Estos hallazgos angiocardiográficos sirven para complementar y confirmar estudios anteriores realizados en material autópsico. Las alteraciones observadas con esta última técnica no proceden aparentemente de procesos agónicos sino que representan el estado vascular durante la vida.

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NICOTINAMIDE THERAPY OF LINGUAL CHANGES IN TUBERCULOUS PATIENTS[1]

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INTRODUCTION

It is well known that the tongue is one of the first organs of the body to reflect signs of nutritional inadequacy. It has been the general opinion that niacin deficiency is probably the most common cause for lingual changes. Sevringhaus and Kyhos (1) reported that, in an unselected group of adults who showed evidence of atrophic lingual changes, the daily administration of 50 mg. of nicotinamide brought about a very definite improvement in most cases, particularly in increased formation of papillae. Several months were usually required for return of the tongue to normal. Little work, however, has been done regarding the possibility of reversal of lingual changes in patients with chronic diseases by a high nicotinamide intake. Cayer and Cody (2) pointed out that during illness, particularly when chronic and associated with fever and weight loss, normal or increased amounts of riboflavin and niacin may be excreted in the urine until the body stores become exhausted.

The following experiment was undertaken to determine the effect of large doses of nicotinamide (oral and parenteral) on the lingual abnormalities observed in a group of patients with advanced active pulmonary tuberculosis.

SELECTION OF PATIENTS AND METHODS OF STUDY

Observations were made on 25 patients who revealed gross lingual evidence of most of the abnormalities commonly ascribed to niacin deficiency. All of them had received a good general diet which in this hospital ranges from 2,500 to 2,700 calories, with an average protein content of 70 to 90 gm. They had also been given supplemental vitamins A, B, C, D in a standard preparation and nourishment between meals, consisting usually of fruit juice or milk. The patients were divided into two groups: (*1*) the treated group who received high doses of nicotinamide orally or intravenously and subsequently a mixture of vitamin B complex and ascorbic acid intramuscularly (Berocca-C)[2]; (*2*) the control group who received placebo pills (lactose).

[1] From the Berthold S. Pollak Hospital for Chest Diseases, Medical Center, Jersey City, New Jersey.

[2] We are indebted to Hoffman-LaRoche, Inc., for supplying the nicotinamide and Berocca C for use in this study. Each 2.0 cc. of the latter preparation contained:

Thiamine hydrochloride	20 mg.
Riboflavin	6 mg.
Nicotinamide	150 mg.
Pyridoxine hydrochloride	6 mg.
Panthenol	6 mg.
Ascorbic acid	100 mg.

In both groups, clinical observations were made prior to, during, and on conclusion of therapy in regard to the degree of redness, magenta hue, soreness, swelling, papillary (filiform and fungiform) atrophy, cross-hatching, and longitudinal or transverse ridging. Ulceration, angular stomatitis, and cheilosis were not seen. Other concurrent studies included Kodachrome photography of the tongue, prints of the tongue using an Evans Blue dye solution according to the method of Di Palma (3), gastric analyses, and the red blood cell and hemoglobin components of the blood count. Therapy for the tuberculous lesion in these patients was carried on with the usual clinical and roentgenologic studies employed for the follow-up evaluation of the progress in each case.

RESULTS

Before recounting the results in detail, reference will be made at this time to some of the salient features of the normal and abnormal tongue which are pertinent to this study. The normal tongue is firm and dense. The bundles of striated muscle and the connective tissue which cause the tongue to swell considerably when inflamed are covered by a dense adherent mucous membrane. The dorsum of the tongue is rough and on it are two main types of papillae: fungiform and filiform. The former are found chiefly at the sides and apex but also are scattered irregularly over the dorsum; the latter cover the anterior two-thirds of the dorsum.

The lingual signs of niacin deficiency vary with the degree of glossitis. Redness, swelling, soreness, transverse or longitudinal ridging, cross-hatching, and papillary atrophy are the chief items to be noted.

Di Palma (3) has advocated a classification of abnormal tongues based on the structure of its surface, namely, the papillae. While the *normal* tongue has intact papillae, the *desquamated* one shows a marked decrease in filiform papillae alone, and the tongue may become red, swollen, and coated. In this phase, return to normal occurs far more often and rapidly than in the second or *atrophic* stage where there is an absence of filiform and a marked reduction also in the fungiform papillae, producing a completely smooth tongue. Di Palma noted two other features commonly found in abnormal tongue prints: (*1*) a cross-hatched pattern due to a thinning out of the mucous membrane so that the underlying fibromuscular network becomes evident; (*2*) and less frequently, longitudinal ridging due to folds in the mucous membrane. Fissuring of the tongue, particularly along the margins, was observed in 20 per cent of the normal cases so that its presence alone cannot be construed as a pathologic finding.

The above criteria appear to have merit, not only in affording a picture of the evolution of glossitis, but also in evaluating the results of therapy. Kruse (4) utilized biomicroscopy, and others have tried both monochromatic and color photography as supplemental objective methods of noting abnormalities. As mentioned above, Di Palma also advocated prints of the tongue on kymograph paper with an Evans Blue solution. Early in our study, papillary counts were done according to the latter's recommendation but these were subsequently discarded, as the counts were quite variable in the same patient on different

TABLE 1

Lingual Changes in Treated Group

CASE	OBSERVATION PERIOD	DURATION OF THERAPY	TONGUE									CONDITION OF TONGUE	CLINICAL CONDITION	REMARKS
			Redness	Soreness	Swelling	Papillary atrophy		Cross-hatching	Longitudinal ridging	Transverse ridging	Magenta hue			
						Filiform	Fungiform							
		days												
1	A		2+	0	2+	3+	3+	0	0	0	0			
	B	126	0	0	0	3+	2+	0	0	0	+	I	I	
	C	90	0	0	0	+	+	0	0	0	0	I	I	
2	A		3+	+	+	3+	2+	+	3+	+	+			
	B	126	3+	0	2+	4+	4+	+	3+	+	0	W	W	
	C	90	3+	0	0	4+	4+	+	4+	2+	0	W	W	
3	A		+	0	0	2+	2+	0	+	+	0			
	B	126	2+	0	+	4+	4+	2+	+	+	0	W	W	
	C	90	0	0	0	3+	3+	+	0	0	0	I	I	
4	A		2+	0	0	2+	0	0	0	0	0			Had streptomycin, 1 gm. daily,
	B	65	4+	0	0	3+	3+	0	2+	0	+	W	W	for 90 days while receiving
	C	90	+	0	0	+	0	0	0	0	0	I	I	500 mg. nicotinamide orally.
5	A		2+	0	+	2+	2+	0	+	+	0			Had left upper lobectomy for
	B	126	+	0	+	+	+	0	+	2+	0	I	I	pulmonary tuberculosis while
	C	90	0	0	0	+	+	0	0	+	0	I	I	receiving 100 mg. nicotinamide orally. Discharged as arrested case.
6	A	40	3+	3+	2+	3+	3+	4+	4+	2+	2+			Died after 40 days of therapy from extensive pulmonary tuberculosis.
7	A		0	0	+	+	+	0	2+	3+	0			Had recurrence of carcinoma of
	B	126	0	0	+	+	+	0	2+	2+	0	S	S	glans penis which healed after radium therapy.
	C	90	+	0	0	+	+	0	2+	2+	0	S	S	
	D	56	0	0	0	+	+	+	3+	2+	0	W	W	
	E	56	0	0	0	2+	+	2+	4+	2+	0	W	W	

8	A		2+	0	0	3+	2+	0	2+	+	0			
	B	126	3+	0	2+	3+	2+	0	3+	+	+	S	S	
	C	90	2+	0	+	2+	2+	0	2+	+	0	I	S	
	D	56	2+	0	+	2+	2+	0	2+	+	0	S	S	
	E	56	2+	0	+	2+	2+	0	2+	+	0	S	S	
9	A		3+	0	0	2+	+	0	3+	+	0			Had streptomycin, 1 gm. daily, for 30 days during the period when he received 500 mg. of nicotinamide orally.
	B	55	4+	0	+	3+	3+	0	3+	+	0	W	W	
	C	90	2+	0	0	+	+	0	+	0	0	I	I	
	D	56	+	0	0	+	+	0	+	0	0	S	S	
	E	56	+	0	0	+	+	0	+	0	0	S	S	
10	A		2+	2+	2+	3+	3+	3+	2+	3+	+			Died from extensive pulmonary tuberculosis.
	B	126	3+	0	+	4+	4+	3+	2+	3+	+	W	W	
	C	90	4+	0	0	4+	4+	3+	3+	3+	0	W	W	
	D	33	4+	0	0	4+	4+	4+	3+	3+	0	W	W	
11	A		2+	0	+	3+	3+	0	0	0	0			Died from extensive pulmonary tuberculosis (massive hemorrhage).
	B	21	3+	+	2+	4+	4+	0	2+	+	+	W	W	
	C	90	2+	0	0	3+	3+	0	+	+	0	I	I	
	D	28	2+	0	0	3+	0	+	+	+	0	S	S	
12	A		3+	0	2+	2+	0	0	3+	+	0			
	D	56	2+	0	0	+	0	0	2+	+	0	I	S	
	E	56	+	0	0	+	0	0	+	+	0	I	S	
13	A		2+	0	0	2+	2+	0	3+	3+	0			
	D	56	+	0	0	+	+	0	2+	2+	0	I	S	
	E	56	0	0	0	+	+	0	+	2+	0	I	S	
14	A		2+	0	2+	+	3+	0	4+	2+	0			Had right upper lobectomy for pulmonary tuberculosis. Pulmonary tuberculosis now quiescent.
	D	56	+	0	2+	+	3+	0	4+	+	0	S	S	
	E	56	+	0	+	+	3+	0	4+	+	0	S	I	

A. Before therapy.
B. At end of treatment with 100 mg. per day of nicotinamide orally.
C. At end of treatment with 500 mg. per day of nicotinamide orally.
D. At end of treatment with 500 mg. per day of nicotinamide intravenously.
E. At end of treatment with 2 cc. per day of Berocca-C intramuscularly.
I. Improved.
S. Stationary.
W. Worse.

prints taken at the same time. Instead, the prints were scrutinized for a general evaluation of the tongue with especial reference to papillary atrophy, ridging, cross-hatching, and fissuring. Incidentally, we found that satisfactory prints can be made on ordinary mimeograph paper. By this simple technique, serial objective records, which are inexpensive, can be obtained. Color photography of the tongue, we believe, is definitely superior to the prints, particularly in appraising such features as swelling, redness, and coating in the desquamative

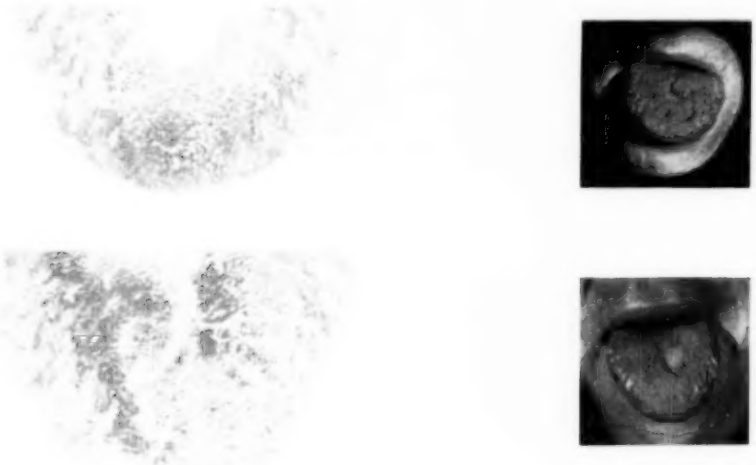

FIG. 1. This figure illustrates lingual improvement with nicotinamide therapy.

B. W. (Case 5), had a nine-year history of pulmonary tuberculosis, with an ineffective left thoracoplasty. Before the start of treatment the tongue was red with moderate filiform and fungiform papillary atrophy, and with marked scalloping at the edges. The patient received 100 mg. of nicotinamide orally for 126 days, followed by 500 mg. orally for 90 days. A left upper lobe lobectomy was performed during this interval of treatment. Patient made an uneventful recovery, and the pulmonary disease became arrested. At the end of 216 days it was noted that the tongue was less red, with regeneration and fungiform and filiform papillae. The marked scalloping, although still present, was definitely improved, in comparison with the pretherapy status.

phase of glossitis. The smooth, atrophic tongue is also better visualized. It should be emphasized, however, that incorrect evaluation may be made if the photography is not done under uniform conditions of exposure and lighting before and after therapy. Needless to say, recourse to color photographic visualization is more costly than the tongue-print technique.

Linqual changes in the treated group (table 1): Eleven patients were given 100 mg. of nicotinamide by mouth over a period of 21 to 126 days, the average being 97 days. One patient (Case 6) died from extensive pulmonary disease on the fortieth day of treatment. Contrasting the status of the tongue before and after

therapy, it was observed that in 6 patients (Cases 2, 3, 4, 9, 10, 11) the lingual abnormalities had increased, manifested by more redness, swelling, ridging, and papillary atrophy. It is important to note, however, that during this interval there was a constitutional decline and progression of the disease visualized in the roentgenograms of the chest in these 6 individuals. Two others (Cases 7 and 8) revealed no significant change in their tongue or clinical condition. In the remaining 2 patients (Cases 1 and 5), improvement in the tuberculous process and general condition was noted during therapy, and similarly in the appearance

FIG. 2. This figure illustrates progression of lingual changes despite therapy.

H. S. (Case 10), 65 years of age, had far advanced pulmonary tuberculosis for four years. He received 100 mg. of nicotinamide by mouth daily for 126 days, 500 mg. for 90 days, and subsequently 500 mg. intravenously daily for 33 days, at which time he died from his extensive disease. Prior to therapy the tongue was moderately red with marked papillary atrophy and cross-hatching on the anterior third of the dorsum of the tongue which gradually became worse despite the high nicotinamide intake. Shortly before his death, the tongue was beefy bright red with complete papillary atrophy. A deep central fissure was present. Cross-hatching was somewhat less prominent.

of the tongue. Reduction in redness and swelling were most evident, while increased papillary growth was less apparent.

To determine the effect of increasing the dosage, the 10 surviving patients were then placed on a regimen of 500 mg. of nicotinamide daily for 90 days. Evaluation of the results at the end of this time indicated that 2 patients (Cases 2 and 10) showed aggravation of their previous lingual abnormalities which now included complete papillary atrophy visible to the naked eye, marked redness, and smoothness. Both of these patients showed clinical deterioration and also failed to respond favorably after the initial study period with 100 mg. One

TABLE 2

Lingual Changes in Control Group

CASE	OBSERVATION PERIOD	TONGUE									CONDITION OF TONGUE	CLINICAL CONDITION	REMARKS
		Redness	Soreness	Swelling	Papillary Atrophy: Filiform	Papillary Atrophy: Fungiform	Cross-hatching	Longitudinal ridging	Transverse ridging	Magenta hue			
1	A	+	0	0	2+	2+	0	0	0	0			
	B	+	0	+	+	+	0	0	0	0	I	I	
	C	0	0	0	+	+	0	0	0	0	I	I	
2	A	+	0	0	3+	3+	0	3+	2+	0			
	B	+	0	0	+	+	0	2+	+	0	I	S	
	C	+	0	+	2+	2+	0	2+	2+	0	W	S	
3	A	4+	0	+	3+	3+	0	2+	+	+			
	B	3+	0	+	2+	2+	0	2+	0	0	I	I	
	C	2+	0	0	+	+	0	2+	0	0	I	I	
4	A	4+	0	0	4+	4+	3+	+	2+	0			
	B	4+	0	0	4+	4+	3+	+	2+	0	S	S	Died from extensive pulmonary tuberculosis at end of observation period B.
5	A	3+	0	2+	3+	3+	0	+	3+	0			
	B	2+	0	0	2+	2+	0	0	0	0	I	I	Died a few days after completion of observation period C.
	C	2+	0	0	3+	3+	+	+	3+	0	W	W	
6	A	4+	0	0	4+	4+	0	2+	+	0			
	B	3+	0	+	3+	2+	0	0	+	+	I	I	
	C	2+	0	0	2+	2+	0	0	0	0	I	I	
7	A	2+	0	0	3+	3+	0	+	3+	0			
	B	+	0	+	2+	2+	0	2+	2+	0	I	I	
	C	+	0	0	+	+	0	2+	+	0	I	I	
8	A	+	0	0	2+	2+	0	0	+	0			Died after 122 days of observation.
	B	4+	0	0	4+	4+	0	0	+	0	W	W	
9	A	3+	0	+	3+	3+	0	0	+	0			
	B	+	0	+	2+	2+	0	+	2+	0	I	I	
	C	0	0	+	+	+	0	+	+	0	I	I	
10	A	3+	+	+	4+	4+	0	3+	+	4+			Died after 22 days of observation.
	B												
11	A	3+	0	+	4+	4+	0	2+	2+	0			Died after 70 days of observation.
	B												

A. At the beginning of observation B. At the end of 126 days of observation C. At the end of 216 days of observation

I. Improved S. Stationary W. Worse

patient (Case 7) showed no change either in his tongue or pulmonary status. Two patients (Cases 1 and 5) maintained their continued improvement following the 100 mg. course of treatment, while the lingual status of 5 others (Cases 3, 4, 8, 9, 11) was better than it had been earlier, showing increased papillary regeneration (both fungiform and filiform). Again, it is noteworthy that 6 of the patients also exhibited a more favorable clinical course, while in the seventh patient the pulmonary lesion was stationary.

The question then presented itself whether the parenteral route of administration might be superior to the oral one. Five of the original group now received 500

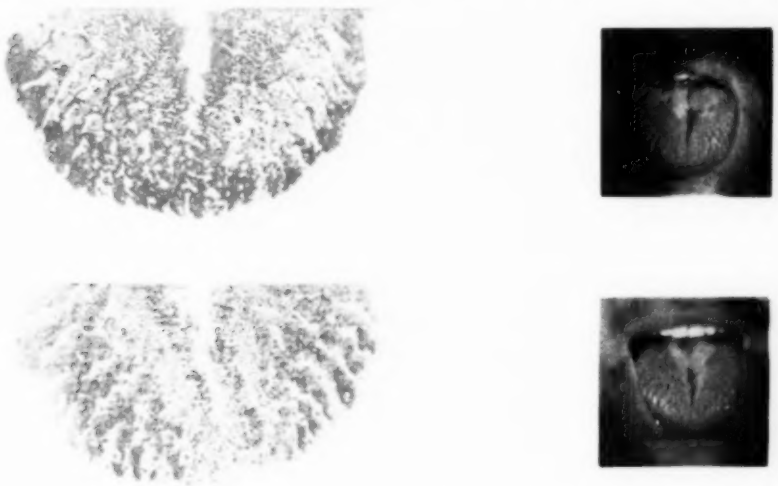

FIG. 3. A patient from the control group in whom lingual improvement occurred.

A. M. (Case 7), 27 years of age, had moderately advanced pulmonary tuberculosis. Originally the tongue showed moderate redness, slight atrophy of the filiform papillae in the center, and marked scalloping at the edges. Placebo medication was continued for 216 days, at the end of which time the tongue was definitely less red. Some regeneration of the filiform papillae was noted in the center, and the marked scalloping became definitely less marked. During this same interval, the patient exhibited definite improvement of his pulmonary disease with closure of the cavity and sputum conversion.

mg. of nicotinamide intravenously each day. The remaining 5 patients refused daily venipunctures so that 3 new patients with abnormal tongue patterns were selected. With 2 exceptions, therapy was continued for 56 days. Two patients (Cases 10, 11) died from extensive tuberculosis 28 and 33 days after the start of intravenous medication. One patient (Case 7) revealed increased papillary atrophy of the tongue and constitutional decline. Two patients (Cases 12 and 13) showed less redness and central papillary regeneration while the pulmonary status was essentially the same. The remaining 3 patients (Cases 8, 9, 14) presented no significant lingual or other clinical change.

The surviving 6 patients were given Berocca-C (2.0 cc. daily) intramuscularly for 56 days. The purpose of this phase of the experiment was to determine whether the combination of the major components of the vitamin B complex together with ascorbic acid might hasten or accentuate a favorable effect. Two patients (Cases 12 and 13) continued to show lingual improvement, although

TABLE 3

Gastric Acidity and Hematologic Observations in Treated Group

CASE	TIME OF OBSERVATION	GASTRIC ACIDITY (UNITS)				BLOOD	
		Fasting		30 Minutes after Histamine		Hemoglobin (gm. per 100 cc.)	Erythrocyte Count (millions per cu. mm.)
		Free	Total	Free	Total		
1	X	18	26	80	90	110	5.5
	Y	3.3	5.3	50	57	106	5.2
2	X	0	5.5	28	40	110	5.4
	Y	—	—	—	—	106	5.2
3	X	—	—	—	—	76	3.8
	Y	—	—	—	—	68	3.4
4	X	0	3.8	42	50	78	4.0
	Y	0	5	46	60	84	4.1
5	X	—	—	—	—	100	5.3
	Y	—	—	—	—	100	4.9
6	X	—	—	—	—	94	4.9
	Y	—	—	—	—	—	—
7	X	0	8	0	10	96	4.8
	Y	0	3	0	14	90	4.7
8	X	0	11	6.1	17	86	4.3
	Y	0	8	12	22	90	4.7
9	X	0	23	74	86	84	4.2
	Y	0	15	51	67	106	4.9
10	X	0	10	0	12	88	4.4
	Y	0	9.2	0	20	80	4.1
11	X	0	1	0	8	96	4.7
	Y	0	14	2.8	14	96	4.9
12	X	0	23	70	106	109	4.9
	Y	0	8	95	106	114	5.8
13	X	0	10.4	72	97	104	5.1
	Y	14	40	78	102	98	4.9
14	X	10	48	75	85	90	4.7
	Y	10	24	96	110	100	4.8

X. Before therapy
Y. After therapy

the clinical condition was unchanged. In Case 7, the tongue appeared worse with increased swelling and ridging despite this therapy. The other 3 patients (Cases 8, 9, 14) showed no significant alterations in the clinical picture or lingual abnormalities.

Lingual changes in the control group (table 2): Of the 11 patients in this cate-

gory receiving placebo medication, 3 patients (Cases 8, 10, 11) died 122, 22, and 70 days, respectively, from the beginning of observation. One patient (Case 10) was followed for too short an interval to make any definite statement possible, but two others (Cases 8 and 11) showed more papillary atrophy, swelling, and transverse ridging of the tongue. One other patient (Case 4) revealed no change, while the tongues in the other 7 patients showed improvement in the appearance of more papillae and lessened redness and swelling. Six of this group were improved clinically and one was unchanged in this respect during the 126 days

TABLE 4

Gastric Acidity and Hematologic Observations in Control Group

CASE	TIME OF OBSERVATION	GASTRIC ACIDITY				BLOOD	
		Fasting		30 Minutes after Histamine		Hemoglobin (gm. per 100 cc.)	Erythrocyte Count (millions per cu. mm.)
		Free	Total	Free	Total		
1	X	0	4	48	68	48	2.5
	Y	0	16	22	48	62	3.4
2	X	0	4.8	13	20	94	4.6
	Y	0	8	15	24	98	4.6
3	X	0	6.4	55	65	100	5.1
	Y	6	15	75	88	101	5.1
4	X	—	—	—	—	88	4.6
	Y	—	—	—	—	80	4.4
5	X	2.7	12	41	49	90	4.5
	Y	0	15	34	46	70	3.5
6	X	—	—	—	—	82	4.0
	Y	—	—	—	—	82	4.2
7	X	0	5.9	12	16	122	6.1
	Y	17	31	25	34	110	
8	X	0	12	15	18	74	3.9
	Y	—	—	—	—	74	3.7
9	X	—	—	—	—	114	5.7
	Y	—	—	—	—	110	5.0
10	X	—	—	—	—	86	4.4
	Y	—	—	—	—	—	—
11	X	—	—	—	—	58	3.0
	Y	—	—	—	—	—	—

X. Before therapy
Y. After therapy

of observation which paralleled the group of cases treated with 100 mg. of nicotinamide.

The surviving 8 patients were followed for another three months *pari passu* with the 10 treated patients who received 500 mg. of nicotinamide orally daily. Five patients (Cases 1, 3, 6, 7, 9) showed constitutional and lingual improvement. Two (Cases 2, 5) became worse in these respects, and one patient died early in this second period. Observation of the control cases was then discontinued after a total period of seven months.

It should be mentioned that in not a single case of either the treated or control group did the tongue revert to normal during the period of this study.

Gastric acidity and hematologic observations (tables 3 and 4): It has been stated (5) that the gastric juice is normally an important element in the extraction of iron and vitamins from their natural food products. Hypochlorhydria is commonly encountered in chronic debilitating diseases such as tuberculosis. Under such circumstances, it is conceivable that there might be some interference with the proper utilization of niacin, for example, even though the oral intake were adequate or even excessive. Gastric analyses, using the histamine technique, were done in a total of 17 patients, of whom 3 (Cases 7, 10, 11) in the treated group showed achlorhydria which persisted throughout the course of their treatment. Five revealed hypochlorhydria, 2 in the treated group (Cases 2 and 8) and 3 among the controls (Cases 2, 7, 8), with no change in the follow-up tests. The remaining 9 patients (6 treated and 3 controls) had normal values of gastric acidity. The status of the anemia in all 4 cases remained unchanged throughout the entire period of treatment. In the control group, 2 patients had mild anemia; two others, moderate anemia; and one, severe secondary anemia before treatment. In one of the patients with mild anemia, progression of the anemia occurred; and in the patient with severe anemia, improvement was noted after treatment.

COMMENT

The vitamin requirements during illness are unknown. In the management of patients with tuberculosis, it is the usual custom for the phthisiologist to prescribe supplementary vitamin preparations. This practice probably stems from the general empiric concept that vitamins afford supportive therapy in infections. Malnutrition, especially that incident to chronic diseases such as active pulmonary tuberculosis, may be the result of one or more processes: (a) toxic destruction of protein which is the direct effect of destruction of tissue; (b) diminished intake of food due to lack of appetite; (c) decreased utilization of some food products with or without decreased absorption; (d) increased excretion of vitamins.

The physician usually looks at the patient's tongue to determine whether it is coated, dry, or moist, as an index of the state of hydration. Closer examination also should be made for the lingual and oral stigmata of associated nutritional deficiency. Insufficient attention is given to such lesions. Although niacin deficiency is undoubtedly an important factor in glossitis, it may often be only *one* of the deficiencies responsible for the changes (5, 6, 7). These have also been reported in association with deficiencies in riboflavin, pyridoxine, and biotin (8, 9, 10). In addition, Ruskin (11) has emphasized the interrelationship in metabolism between amino acids and factors of the vitamin B complex. The latter combine with specific proteins to form coenzymes which in turn participate in the hydrogen transfer in the breakdown of carbohydrates and liberation of energy. If either the essential amino acids or the vitamins are absent, the necessary enzyme systems will not be completed.

The results of our experiment, however, definitely indicate that little can be accomplished by the therapy used in significantly improving the glossitis in

active advanced pulmonary tuberculosis which is progressive in nature. Quiescence or regression of the tuberculous process appears to be a necessary prerequisite for such lingual improvement. Tuberculous enteritis, in particular, merits prompt attention. Fortunately, streptomycin is highly efficacious in the control of gastrointestinal symptoms which can seriously interfere with the absorption and utilization of food products.

SUMMARY AND CONCLUSIONS

A study was carried out in a group of patients with active, advanced tuberculosis to determine primarily the effect of large doses of nicotinamide on abnormal lingual changes which are commonly attributed to a deficiency of niacin. Several patients also revealed a magenta hue of the tongue which is usually ascribed to a lack of riboflavin.

The important finding was a very close parallelism between the clinical and/or roentgenologic course and the lingual status for both the treated and untreated cases. One patient (Case 6) in the former group and 2 (Cases 10 and 11) among the controls were omitted from the following final summary of results because of the relatively short period of observation which terminated in death. Thirteen patients in the treated group received nicotinamide (100 mg. or 500 mg. orally or 500 mg. intravenously). Some received, in addition to or in place of this, an intramuscularly administered preparation (Berocca-C) containing the chief components of the vitamin B complex plus ascorbic acid. The minimum period of treatment was 112 days; the maximum, 328; and the average, 204 days. At the end of therapy, the over-all evaluation showed lingual improvement in 6 patients, consisting chiefly of reduction in redness and swelling and papillary regeneration. There was no change in 2 patients and progression of glossitis in 5 patients. Nine with essentially similar lingual findings were given placebo medication. The minimum observation period for this group was 122 days; the maximum, 216; and the average, 196 days. Five patients revealed improvement in the glossitis comparable to the treated patients, 2 showed no improvement, and in 2 the condition became worse. Control of the tuberculosis in both groups appeared most essential in achieving lingual improvement.

It is emphasized, however, that closer attention should be given in these cases to the tongue and oral cavity for signs of nutritional deficiency. Permanent objective serial records can be obtained by means of color photography and the tongue-print technique of Di Palma. The relative merits of each are evaluated. While niacin deficiency is a factor in glossitis, *balanced* and *complete* nutritional therapy is essential, with special reference to a high protein intake. Deficiencies of single vitamins are rare in clinical practice. Since the most commonly encountered deficiencies are those of the B complex and since their function is interrelated, it seems preferable to administer this group of vitamins together.

SUMARIO Y CONCLUSIONES

Nicotinamidoterapia de la Patología Lingual en los Tuberculosos

Un estudio verificado en un grupo de casos avanzados y activos de tuberculosis proponíase primordialmente determinar el efecto de grandes dosis de nicotina-

mida sobre las anomalías linguales que se suelen imputar a deficiencia de niacina. Varios enfermos revelaban además un tinte magenta de la lengua que se atribuye generalmente a falta de riboflavina.

El hallazgo importante consistió en el estrechísimo paralelismo entre la evolución clínica y/o roentgenológica y el estado lingual tanto en los casos tratados cuanto en los no tratados. Del siguiente sumario final de los resultados omitiéronse el Caso 6 entre los primeros y los Casos 10 y 11 entre los testigos, debido a período relativamente breve de observación, que culminó en la muerte. Trece casos del grupo tratado recibieron nicotinamida (100 ó 500 mg. oralmente o 500 mg. endovenosamente) y/o, en algunos casos, por vía intramuscular, una preparación (Berocca-C), que contiene los principales componentes del complejo vitamínico B y además ácido ascórbico. El período mínimo de tratamiento comprendió 112 días, el máximo, 328, y el promedio, 204 días. Al terminar el tratamiento, la justipreciación global reveló mejoría lingual en 6 casos (consistiendo la misma principalmente en disminución del enrojecimiento y edema y en regeneración papilar), falta de modificación en 2 y agravación de la glositis en 5. En 9 casos con hallazgos linguales en el fondo similares se administró un placebo como medicación. En este grupo, el período mínimo de observación duró 122 días; el máximo, 216; y el promedio, 196 días. Cinco casos mostraron en la glositis una mejoría comparable a la de los pacientes tratados, 2 no mostraron mejoría, y en 2 se empeoró el estado. En ambos grupos, el dominio de la tuberculosis pareció ser lo más esencial para obtener mejoría de la lengua.

No obstante, recálcase que, en estos casos, hay que prestar mayor atención a la lengua y la cavidad bucal en busca de signos de deficiencia nutritiva. Pueden obtenerse permanentes registros objetivos en serie por medio de la cromofotografía y la técnica glosográfica de DiPalma. Compáranse aquí los relativos méritos de ambos sistemas. Si bien la deficiencia de niacina constituye un factor en la glositis, una trofoterapia *equilibrada* y *completa* resulta indispensable con referencia en particular a una ingestión alta de proteína. En la práctica clínica son raras las deficiencias de vitaminas aisladas. Como las deficiencias encontradas más habitualmente son las del complejo B y como la función de las mismas se halla entrelazada, parece preferible administrar ese grupo de vitaminas en conjunto.

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THE CELLULAR AND IMMUNOLOGICAL REACTIONS IN RABBITS INFECTED WITH HISTOPLASMA CAPSULATUM[1, 2]

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INTRODUCTION

In recent years substantial contributions have been made to the clinical picture of histoplasmosis (17). This disease is regarded as a generalized fungus infection which is incited by the slightly acid-fast (20) yeastlike phase of *Histoplasma capsulatum*. The organism affects primarily the cells of the reticuloendothelial system, and thereby induces a number of systemic changes (9). Although the fungus bears no relationship to the tubercle bacillus, the clinical aspects of the infections caused by the two organisms have many features in common. The most important of these features are the lung calcifications which have been so widely observed in individuals with negative tuberculin but positive histoplasmin skin tests (2, 15, 18). As we now know, this has been the cause of much confusion.

Since many details of the histoplasma infection are still obscure, an experimental approach seemed to offer possibilities for further elucidation of the problem. It is the purpose of this paper to report observations made in rabbits infected by various routes with several strains of *Histoplasma capsulatum* with reference to their cellular and immunological reactions studied at different intervals.

Methods

Five groups of rabbits, weighing four to five pounds, were studied. Each group consisted of 3 to 5 test animals and a control. During a control period prior to inoculation of the rabbits, appropriate observations were made to establish their normal condition. The test animals of the individual groups were then infected as specified below. The animals were kept in individual cages and fed with the usual pellets, greens, and water.

For infection, four strains of *Histoplasma capsulatum* were used. Two strains, No. 701 (obtained from Dr. A. Howell) and No. 650 (obtained from Dr. M. Tager) were injected in their mycelial form. The organisms for injection had been harvested from four to five cultures grown at room temperature for ten to fourteen days on potato-dextrose agar. The mycelial growth in each tube was scraped from the medium, ground in a mortar, and suspended in 5 ml. of isotonic solution of sodium chloride. The suspensions were then combined, homogenized, and allowed to settle for a short time to eliminate coarse particles. Three to five milliliters of the milky supernatant were injected into the experi-

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mental animals using a 24-gauge needle. On microscopic examination short mycelial elements were seen in the fluid. Two other strains, No. 1066 (obtained from Dr. N. Conant) and No. HI-4882 (obtained from Miss A. Snyder) were used in their yeast form. The change from the mycelial to the yeast form was accomplished by growing the organisms on successive transfers on slightly modified Francis medium slants at 37°C.[5] After four to five days of incubation, the typical yeastlike growth was then easily dispersed in 5 ml. of saline and required no special manipulation preparatory to injection. Two milliliters of the suspension were used for injection of the animals.

During the course of investigation, complete blood counts were performed serially on all animals. For the qualitative analysis a supravital staining technique was used[6] (22, 23). Of the group in which the cells of the peritoneal cavity were studied, the component animals were sacrificed by nembutal narcosis at different intervals after infection. Samples were taken from the peritoneal fluid, the omentum, and the abdominal and mammary lymph nodes for supravital staining. Seventeen animals were autopsied and their tissues fixed in Zenkerformol solution or in 10 per cent formalin for histologic study. In the animals injected subcutaneously, the affected layer of skin was excised. A part of the excised tissue was spread over a slide for supravital staining and the other part used for histologic examination.

Immunologic studies included skin testing of the animals with histoplasmin 1:500 (furnished by the Illinois State Department of Health Laboratories) and in one group of animals (Group 3) the complement fixation test which had been developed while this work was in progress (26, 29). In the latter test, the final volume was 3.0 ml. containing serum (0.2 ml.), antigen (0.2 ml. of 1:100 dilution of histoplasmin), complement (2 full units in 1 ml.), hemolysin (2 units in 0.5 ml.), and sheep erythrocytes (0.5 ml. of a 2 per cent suspension).

RESULTS

Cellular reactions: Each of two groups of rabbits was infected with the mycelial form of *Histoplasma capsulatum*. Group 1 was injected with Strain No. 701, and Group 2 with Strain No. 650. The first group received both intravenous (2 ml.) and intraperitoneal (3 ml.) injections within an interval of a few minutes, whereas the second group received intravenous (3 ml.) injections only. Groups 1 and 2 will be presented together, since the results were closely similar.

Changes in the blood first became apparent between the fifth and sixteenth days after infection and lasted from six to twenty-eight days (tables 1 and 2, figures 1 and 2). Although the general picture was the same in both groups, the reactions in the first group seemed to be more pronounced. There was a decrease in concentration of hemoglobin, an increase in the total leukocytes, a relative and absolute increase in neutrophilic granulocytes. There was a marked increase in monocytes. The lymphocytes showed a relative but not an absolute decrease. With the increase in the total number of monocytes, more and more stimulated

[5] In addition to temperature, reduced oxygen tension, cysteine, pH, and moisture, all of which have been advocated as important factors in the transformation (4, 25), the authors concluded from their own experience that rapid transfers (every second day) carrying over the soft, mushy parts of the early growth are most successful in effecting this transformation.

[6] Comparative studies with this technique and the Wright staining method have revealed the superiority of the supravital method for our purpose.

TABLE 1

GROUP 1

Blood Changes after Intravenous and Intraperitoneal Infection of Rabbits with the Mycelial Form of Histoplasma Capsulatum (No. 701)

RABBIT NUMBER	PERIOD OF OBSERVATION	WEIGHT CHANGES	TOTAL LEUKOCYTES PER CU. MM.			POLYMORPHONUCLEAR LEUKOCYTES PER CU. MM.			LYMPHOCYTES PER CU. MM.			MONOCYTES PER CU. MM.			ERYTHROCYTES MILLION PER CU. MM.			HEMOGLOBIN GM. PER 100 CC.		
			Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average
		gm.																		
	Normal	2,098	7,050	8,500	7,750	1,800	4,867	2,779	2,145	4,675	3,521	412	680	558	6.62	7.14	6.96	14.4	15.4	14.7
1	After infection:																			
	Reaction phase	2,610	9,050	20,500	15,514	3,348	8,816	6,541	1,824	5,547	3,534	1,267	6,195	2,982	5.57	7.10	6.26	10.1	12.5	11.8
	Postreaction phase	2,778			7,450			2,379			3,585			704			7.60			14.15
	Normal	2,271	8,650	11,200	9,660	3,024	5,376	3,911	3,546	5,008	4,435	346	672	526	6.32	7.31	6.932	12.6	15.0	14.0
2	After infection:																			
	Reaction phase	2,413	9,850	14,100	11,700	5,319	7,896	6,961	1,470	3,152	2,425	591	3,102	1,677	5.58	6.42	6.004	12.1	14.6	13.2
	Postreaction phase	2,976	6,950	11,550	9,350	2,551	4,389	3,427	2,710	5,481	4,297	417	661	550	6.04	7.67	7.057	13.6	15.2	14.3
	Normal	2,098	7,000	9,900	8,062	2,538	3,237	2,952	3,220	5,247	3,902	280	581	377	6.23	6.91	6.577	12.9	14.6	13.8
3	After infection:																			
	Reaction phase	2,948	6,750	13,350	9,120	2,176	5,206	3,951	1,822	2,992	2,155	476	4,405	1,918	4.74	5.75	5.178	9.8	12.1	10.6
	Postreaction phase	3,260	5,550	7,300	6,650	2,331	3,942	3,123	1,290	2,774	2,057	146	967	572	5.73	7.82	6.565	12.0	14.9	14.2
	Normal	2,098	7,050	10,750	8,650	2,376	4,676	3,233	2,608	6,020	4,045	189	696	371	6.09	7.51	6.815	13.0	15.0	14.1
4	After infection:																			
	Reaction phase	2,466	9,100	17,350	14,980	2,730	10,880	8,071	2,550	4,914	3,384	728	3,234	2,307	6.08	7.01	6.925	12.5	13.9	12.8
	Postreaction phase	2,548	8,700	9,450	9,100	3,393	6,130	5,158	1,281	3,828	2,364	661	823	755	6.76	7.77	7.136	12.8	14.5	13.9
5	Control	2,041 2,778 2,891	7,050	10,950	8,526	2,093	4,136	2,979	1,903	5,764	4,156	216	752	483	5.21	7.39	6.626	12.5	15.6	13.9

TABLE 2

GROUP 2

Blood Changes after Intravenous Infection of Rabbits with the Mycelial Form of Histoplasma Capsulatum (No. 650)

RABBIT NUMBER	PERIOD OF OBSERVATION	WEIGHT CHANGES	TOTAL LEUKOCYTES PER CU. MM.			POLYMORPHONUCLEAR LEUKOCYTES PER CU. MM.			LYMPHOCYTES PER CU. MM.			MONOCYTES PER CU. MM.			ERYTHROCYTES MILLION PER CU. MM.			HEMOGLOBIN GM. PER 100 CC.		
			Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average
		gm.																		
7	Normal	1,758	6,050	19,050	9,688	3,151	12,382	5,678	1,554	3,619	2,321	532	2,380	1,192	4.77	7.29	5.98	10.1	13.4	11.8
	After infection:																			
	Reaction phase	1,928	8,150	23,450	17,894	3,423	14,858	9,586	938	4,221	2,877	1,304	7,847	4,297	4.91	6.54	5.817	10.3	12.0	11.1
	Postreaction phase	2,523			14,475			8,267			3,194			2,026			5.16			11.6
8	Normal	1,701	5,500	13,850	9,425	990	8,978	4,945	1,608	3,462	2,760	236	1,876	790	4.89	7.51	6.279	11.6	14.8	12.8
	After infection:																			
	Reaction phase	1,871	11,800	19,300	14,200	5,251	13,317	8,697	1,897	4,000	2,827	632	2,950	1,576	6.26	7.43	6.795	10.7	14.6	12.7
	Postreaction phase	2,495	10,600	17,900	13,516	6,254	12,351	8,692	2,332	3,580	2,974	895	1,060	852	5.97	6.75	6.42	12.7	14.3	13.4
9	Normal	2,240	5,600	12,500	8,268	2,085	8,500	4,619	1,345	4,284	2,414	300	1,000	686	4.13	6.27	5.495	9.5	14.0	11.1
	After infection:																			
	Reaction phase	2,240	4,450	19,100	10,833	1,424	11,460	5,273	2,002	5,730	3,092	311	3,912	1,576	4.47	6.53	5.326	9.7	11.7	10.6
	Postreaction phase	3,033	8,050	11,150	9,633	3,300	7,024	4,928	2,898	3,298	3,031	557	1,127	820	5.09	6.43	5.553	11.1	15.1	12.4
10	Control	2,495																		
		2,863	5,600	11,700	7,992	2,117	6,903	4,373	1,232	3,869	2,092	360	1,232	666	4.35	6.48	5.541	9.5	13.6	11.4
		3,600																		

forms appeared. These blood changes did not persist, however, and within a variable period of time (eleven to forty-four days) the blood picture returned to normal. The injected microorganisms were at no time demonstrable in the supravital preparations. As will be discussed later, all of the animals developed skin sensitivity as shown by the histoplasmin test.

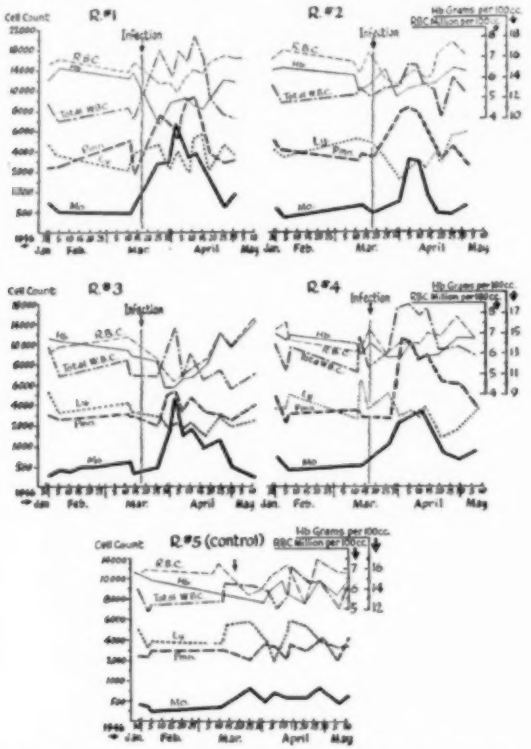

FIG. 1. Tracings of blood changes in animals of Group 1

In spite of the above reactions, the animals in neither group displayed clinical signs of the disease and, indeed, they gained in weight. The question then arose whether a complete restoration to normal had occurred or a latent chronic focus of infection had developed as the continued skin sensitivity seemed to indicate. To test this latter possibility, eight weeks after the first injection the first group of animals were reinjected with different amounts of organisms of the same strain (No. 701). The result was dramatic. In inverse proportion to the amount used, the animals succumbed in from a few minutes to several hours in an acute or somwehat delayed anaphylactic type of shock. The histologic studies of these

animals revealed progressive signs of anaphylactic shock corresponding to the elapsed time between reinjection and death. From slight to marked interstitial edema, hemorrhages, and necrosis were demonstrable in the lungs. The livers, bone marrows, and other organs seemed to be normal in structure. The spleens showed definite damage of the germinal centers with atrophy of these centers and dilatation of the sinusoids. Animal No. 1 showed a tubercle of the lung with epithelioid cells and giant cells. The spleen of this animal also contained giant cells.

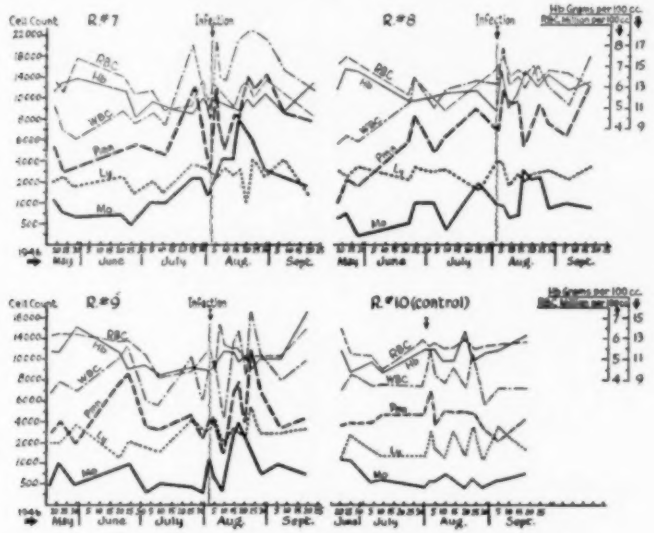

FIG. 2. Tracings of blood changes in animals of Group 2

The second group was kept under observation for approximately one year. The animals remained in good health throughout this period. Chest roentgenograms showed normal lung fields. The animals were sacrificed and their organs examined histologically. The findings reflected a regressing process. A few fibrotic areas with infiltration of mononuclear cells were seen in the livers, spleens, and lymph nodes. In none of the cells could the presence of *H. capsulatum* be recognized.

An entirely different reaction was obtained with the yeast phase of the fungus in the third group of animals (Group 3). Two of these animals (R-20 and R-21) were infected with strain HI-4882, and three other animals (R-22, R-23, and R-24) with strain HC-1066. Injection of the microorganisms were given intravenously and intraperitoneally in rapid succession as in the first group, using a total of 2 ml. of yeast suspension for each animal (table 3, figure 3).

As may readily be seen, 4 animals reacted with changes in the peripheral

TABLE 3

GROUP 3

Blood Changes after Intravenous and Intraperitoneal Infection of Rabbits with the Yeast Form of Histoplasma Capsulatum (No. 4882, No. 1066)

RABBIT NUMBER	PERIOD OF OBSERVATION	WEIGHT CHANGES	TOTAL LEUKOCYTES PER CU. MM.			POLYMORPHONUCLEAR LEUKOCYTES PER CU. MM.			LYMPHOCYTES PER CU. MM.			MONOCYTES PER CU. MM.			ERYTHROCYTES MILLION PER CU. MM.			HEMOGLOBIN GM. PER 100 CC.		
			Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average
		gm.																		
20	Normal	2,482–2,620	9,100	12,100	10,640	3,367	6,352	4,991	4,366	4,924	4,655	603	944	819	6.32	7.25	6.828	12.00	13.65	12.83
	After infection	2,755–3,075	6,100	19,400	11,234	3,416	11,037	6,011	1,132	7,760	3,376	523	3,240	1,718	5.16	6.72	6.114	10.45	13.75	11.87
21	Normal	2,322–2,633	10,550	13,450	12,300	4,220	6,655	5,489	2,871	6,566	4,729	526	2,284	1,269	6.38	7.14	6.67	12.20	13.35	12.67
	After infection	2,819–3,745	8,100	24,150	14,358	4,374	15,576	7,816	2,025	6,762	4,243	115	4,468	1,508	6.05	7.51	6.794	10.80	15.00	13.43
22	Normal	2,652–2,858	8,350	11,750	10,000	3,165	5,451	3,902	3,363	6,150	4,877	300	700	548	4.94	5.57	5.366	10.15	11.80	11.08
	After infection	3,035–3,572	9,050	33,500	15,729	3,116	13,735	6,843	3,062	15,410	5,984	1,048	4,020	2,198	4.88	7.46	5.629	9.55	12.20	10.49
23	Normal	2,421–2,510	6,750	11,000	8,480	3,075	6,868	5,214	1,350	3,320	2,352	371	675	539	7.32	7.88	7.51	13.15	14.40	13.92
	After infection	2,300–2,935	6,700	19,800	12,850	3,781	14,652	8,414	897	4,337	2,564	616	3,470	1,532	5.11	7.61	6.44	10.15	12.95	11.63
24	Normal	2,987–3,205	7,300	10,200	8,380	2,445	3,774	3,139	3,325	5,661	4,676	146	531	320	5.85	6.02	5.94	12.40	13.75	13.02
	After infection	3,170–3,592	8,750	11,900	10,390	4,812	6,783	5,554	2,712	3,496	3,153	1,093	1,904	1,502	4.88	5.66	5.302	10.97	12.20	11.39
25	Control	2,933–3,400	8,300	13,100	10,463	3,319	5,806	4,677	3,320	6,210	4,733	262	932	514	6.29	7.945	7.114	12.2	13.7	13.13

blood much sooner than those of the first two groups, i.e., within two to three days. There were rapid fluctuations of all the white blood cell elements, and in all animals there was a more or less pronounced monocytic response. During the clinically evident exacerbations, the hemoglobin concentration and erythrocyte counts declined and the animals lost considerable weight. Although strain

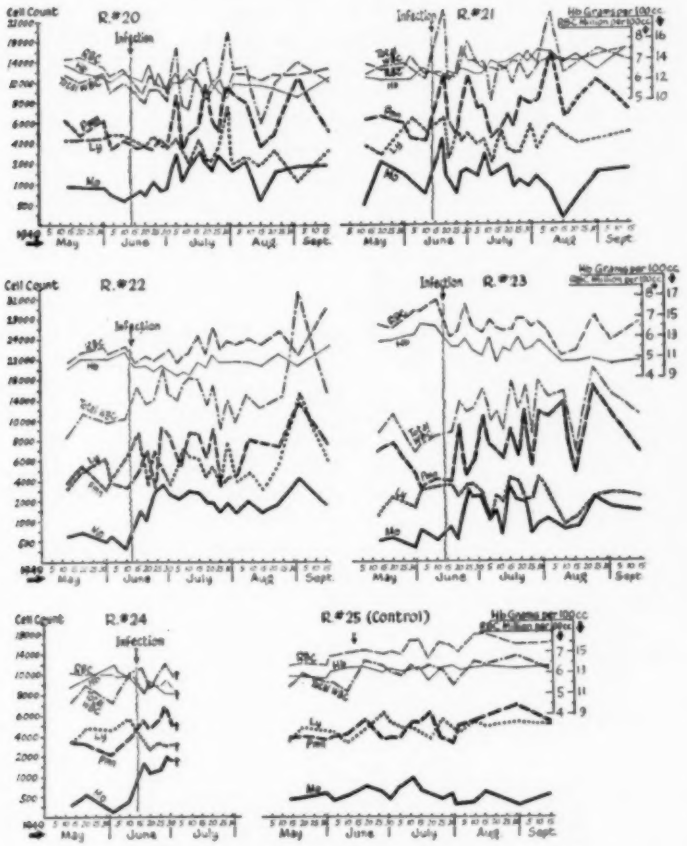

FIG. 3. Tracings of blood changes in animals of Group 3

HI-4882 was a recently isolated one and strain HC-1066 had been maintained in the laboratory for quite some time, the latter proved to be more virulent. Two of the 3 animals infected with this strain died; R-24, after 23 days, and R-23, after 129 days. This might indicate that there are differences in virulence among the various strains, but these differences are not dependent on the phase (yeast or mycelial) in which the organism is introduced. In both instances, the

TABLE 4

GROUP 4

Relative Changes in the Cellular Elements of the Peritoneal Fluid, Omentum, and Lymph Nodes after Intraperitoneal Infection with the Mycelial Form of Histoplasma Capsulatum (No. 650)

RABBIT NUMBER	TIME ELAPSED AFTER INFECTION	CELLULAR ELEMENTS IN:	POLYMORPHONUCLEAR LEUKOCYTES	BASOPHILS	EOSINOPHILS	* LYMPHOCYTES	MONOCYTES	STIMULATED MONOCYTES	CLASMATOCYTES	EPITHELIOID CELLS	GIANT CELLS	SEROSAL CELLS	UNCLASSIFIED	MACROSCOPIC MILK SPOTS
11	2 days	Peritoneal fluid (per cent),	0	0.3	2.3	16.3	70.4	0	0	0	0	10.7	0	
		Omentum,		+	+		+	+		+	+	+		+
		Lymph nodes*			+		+		+					
12	1 week	Peritoneal fluid (per cent),	0	0.5	6.5	9.5	51.5	0	6.0	4.0		19.5	2.5	
		Omentum,			+		++		++	+++	++	+		++
		Lymph nodes*			++		+		++					
13	2 weeks	Peritoneal fluid (per cent),	23.6	0.4	4.0	52.4	13.6	2.0	2.6	0	0	1.4	0	
		Omentum,					+++	+++	+++	+++	+++	++		+++
		Lymph nodes*												
14	3 weeks	Peritoneal fluid (per cent),	0	0	0	4.0	78		8.0	3.0	0	7.0	0	
		Omentum,										+		
		Lymph nodes*			+									
15	4 weeks	Peritoneal fluid (per cent),	1	0	7	33.0	45	3	1.0	7.0	2.0	1.0	0	
		Omentum,					+	+		+		++		+
		Lymph nodes*			+		+		+	+†				
16	6 weeks	Peritoneal fluid (per cent),	1	0	0	28.0	58.0	0	7.0	4.0	0	2.0	0	
		Omentum,										++		
		Lymph nodes*			+		+		+	++†	++†			

* In mesenteric and substernal mammary lymph nodes

† In substernal mammary lymph nodes only

number of monocytes were in the ascending stage before the death of the animal, and the fungus was recovered by cultivation from the blood stream. Histologic examination of the tissues of these animals revealed a granulomatous reaction in various organs, and the mononuclear macrophages contained typical intracellular yeast forms of *Histoplasma capsulatum*.

In the remaining animals of the third group (R-20, R-21, R-22) the blood picture gradually returned to normal. They apparently recovered and one visible sign of this was a gain in weight. As we shall see later, however, their histoplasmin sensitivities and positive complement fixation tests persisted.

Since the preceding experiments did not provide any information concerning the initial development of local cellular reactions, a study was made of the omentum and peritoneal fluid after infecting the rabbits intraperitoneally with 3 ml. of mycelial suspension (Group 4). Six rabbits were simultaneously injected into the peritoneal cavity with the mycelial form of the fungus. After two days, eight days, and two, three, four, and six weeks, the induced changes were examined and tabulated (table 4).

Beginning with the second day of observation, the cellular changes in the omentum became apparent with increasing intensity in the animals sacrificed after one and two weeks. The changes consisted of the appearance of macroscopically visible milk spots growing in number and size. Microscopically, these milk spots revealed the presence of an increasing number of monocytes, stimulated monocytes, clasmatocytes, epithelioid cells, and Langhans'-type giant cells with an occasional foreign-body giant cell. The rabbits sacrificed after three and four weeks showed that a gradual regression of the process was occurring with the disappearance from the omentum of the specific cellular elements in the reverse order of their appearance. Finally, six weeks after the infection, the normal aspect of the omentum was restored. Simultaneously, monocytes, epithelioid cells, and epithelioid giant cells appeared in the substernal mammary glands where they subsided last. This reaction in the mammary glands was most pronounced in rabbit No. 16 (sacrificed after six weeks), where in many microscopic fields nests of 8 to 10 epithelioid cells and 2 to 3 giant cells could be seen at the time when the omentum appeared to be practically normal again. The cellular elements in the peritoneal fluid of the different animals seemed to follow the pattern of the omental changes but somewhat overlapped them.

The blood picture prior to sacrifice of the animals did not show any noteworthy alterations. Histoplasma were not recovered from any of the animals studied in this group. Histologic findings support the observations with the supravital technique. The characteristic changes were found in the omenta and lymph nodes. In rabbits Nos. 11, 12, and 13, the omenta revealed necrosis, epithelioid cells and Langhans'-type giant cells; in rabbits Nos. 14, 15, and 16, the findings in the omentum were negative, whereas the epithelioid and giant cells were seen in the substernal mammary glands. With the exception of rabbit No. 15, where the bone marrow showed small accumulations of epithelioid cells, none of the other organs in any of the animals showed any gross pathologic changes.

In the fifth group of rabbits, the effects of local changes were studied in animals

TABLE 5

*Histoplasmin and Complement Fixation Tests in Rabbits**

GROUP	ANIMAL NUMBER	INFECTED WITH STRAIN	DAYS AFTER INFECTION												
			10	15	21	23	25	31	37	59	65	78	132	182	206	243
1	1	No. 701 mycelial form			+			+				+				
	2				+			+				+				
	3				0			0				+				
	4				+			+				+				
	5	Control			0			0				0				
2	7	No. 650 mycelial form		0		+							+			+
	8			0		0							+			+
	9			0		+							+			+
	10	Control		0		0							0			0
3	20	HI-4882 yeast form	0		Negative		0		Slightly positive	Negative	+			Positive		
	21		0		Positive		0		Positive	Positive	+			Positive	Positive +	
	22	HC-1066 yeast form	+		Positive		+		Positive	Positive	+			Positive	Positive +	
	23		+		Positive		+		Positive	Positive						
	24		+		Positive											
	25	Control	0		Negative		0		Negative	Negative	0			Negative	Negative 0	

Before inoculation, skin tests in all animals were negative with histoplasmin and tuberculin; in group 3 the complement fixation test was also negative.

* The results of histoplasmin tests are indicated by + and 0 signs, and those of the complement fixation tests as "positive" and "negative."

injected subcutaneously. For this purpose, a suspension of the mycelial organism (0.5 ml.) was injected into the shaved buttock region. Within 48 hours a local inflammatory focus with necrotic center developed under the unbroken skin. This process slowly progressed until the fifth day at which time the area of the lesion was excised. A thin layer of the subcutaneous tissue was spread over a slide and stained supravitally. Other portions were fixed for histologic examination. The findings on microscopic examination of these preparations consisted of a marked cellular infiltration with leukocytes and monocytes. The normal architecture was maintained, except in the necrotic area where it was completely destroyed. Engulfed yeast forms of the fungus were visible in a few scattered cells of the macrophage type close to the border of the necrotic area.

Recovery of yeast cells from the subcutaneous tissue presents another example of transformation of the mycelial form into the yeast form in living tissues. The presence and identity of the organism in the lesion was further supported by the fact that upon cultivating it *in vitro* on the potato-dextrose agar medium the mycelial form was grown, thereby identifying the organism by its biphasic character. These findings coincide with the more extended observations of Hansmann and Schenken (10). They found also that the local lesions progressed for seven days, following which definite evidence of regression was noted. When they sacrificed these animals after approximately four weeks, the microorganisms were still viable in the lesion but there was no apparent generalized dissemination of the infection. They concluded that the lesions would probably have healed in time in these animals.

Immunological reactions: The skin sensitivity to histoplasmin was tested in Groups 1, 2, 3, and 4 at various intervals;[7] Group 3 was also tested by the complement fixation test (table 5). As may be seen, skin sensitivity appeared after intervals of ten to seventy-eight days. It is obviously difficult to assess the exact time of sensitization. It is worthy of note, however, that in animals infected with the more virulent yeast form (HC-1066) skin tests became positive somewhat sooner than in those infected with the mycelial form. Sensitization of animals in Groups 1 and 2 must have occurred between the fifteenth and twenty-third days after infection. In contrast, in the third group infected with yeast, 3 animals reacted by the tenth day. Nevertheless, there were one or 2 slow reactors in all of the groups studied.

The complement fixation test was positive after twenty-one days. Interestingly, in animal No. 21, this test became positive sooner than the skin sensitivity.

Both tests when once fully developed seemed to persist as far as these observations were carried out (206 days). The persistence of both tests is particularly significant in those instances in which the causative agent was not demonstrable. It provides an indirect but positive evidence of an active infection in the animal host.

[7] The test was not performed more frequently because, at the time of these experiments, it was not yet established to what extent the histoplasmin itself would act as a sensitizing agent. Howell (12) has subsequently shown, however, that diluted histoplasmin repeatedly injected will not sensitize normal animals.

DISCUSSION

In the course of investigations to disclose possible sources of infection with *H. capsulatum*, a series of animals such as dogs (19), cats (14), rats (5, 6, 7), mice (6, 16, 28), and skunks (7) have been found to be spontaneous carriers of the organism. In spite of these findings, the animal of choice for experimental purposes is still not settled. It has been the common experience of those working in this field that the susceptibility to active infection of most laboratory animals, including guinea pigs and rabbits, is very irregular. For instance, Reid and his associates (21) found mice and rabbits insusceptible and only the guinea pig useful for experimental purposes. On the contrary, Tager and Liebow (28), Parsons (16), Ciferri and his associates (3) found mice and rabbits to be more susceptible than guinea pigs. Hansmann and Schenken (10) also failed to produce the infection in guinea pigs, but obtained positive results in rabbits. Recently, Howell (12, 13) found that guinea pigs are relatively resistant to the infection while Allen (1) came to the conclusion that mice and guinea pigs are more susceptible than rabbits. Salvin (26) again found rabbits to be quite useful in his immunologic studies. In view of these discrepancies, the chief reason for choosing rabbits was that they gave us more consistent results, they are more suitable for hematologic studies, and they had been used in similar studies in experimental tuberculosis.

The cellular changes in general were protracted but not permanent in nature, reflecting in all probability the transitory nature of reaction in the hematopoietic tissues of those animals which did not succumb to the infection. The location of these cellular changes varied according to the route of the infection. After intravenous infection, the most characteristic findings were noted in the blood. Hypochromic anemia, leukocytosis, and monocytosis were constantly present. This is somewhat different from what one would expect in the human disease where leukocytosis as well as leukopenia have been reported (17). It should be remembered, however, that the majority of human cases reported with leukopenia were observed only in the terminal stages, whereas the experimental findings represented more directly the initial phases of the infection. After intraperitoneal infection, the changes occurred in the omentum and peritoneal fluid, while the blood remained unaltered. The conspicuous involvement, in the blood and in the omentum, of cells belonging to the monocytic series clearly points to the specific stimulation of the reticuloendothelial system. The same type of reaction has previously been reported in experimental tuberculosis of rabbits (24).

The skin sensitivity appeared somewhat later than the cellular changes but, once fully developed, persisted during the entire year of observation. It is significant that the skin sensitivity develops only after true infection with living fungi and not after immunization with the dead microorganisms (27). That the sensitization was generalized and not limited to the skin alone was demonstrated by the fact that the reinjected animals of the first group died in anaphylactic shock. The possible errors in histoplasmin testing due to cross reactions (8, 11) could be safely disregarded because all animals were tested before infection and were found to be negative.

The above observations were supported by the results of the complement

fixation test recently adapted to histoplasmosis. The fact that in all but one animal it became positive later than the skin test would indicate that the appearance of complement-fixing antibodies is contingent upon the concentration of specific antigens released within the body. That the formation of these antibodies is not dependent upon living microorganisms can be concluded from the high titer of immune serum obtainable by active immunization with killed fungi.

It seems possible that the course of this disease in rabbits is somewhat similar to that which occurs in humans. Neither of these two species is pre-eminently susceptible to histoplasma infection. After coming in contact with the fungus, only a few cases progress to fatal termination. In the surviving cases a balanced equilibrium probably develops between host and fungus. A positive histoplasmin and complement fixation test under such conditions indicates that an infection actually had occurred, and that the fungus is still present within the host.

SUMMARY

In rabbits inoculated with the mycelial form of *H. capsulatum* a generalized, chronic infection was induced, while in those animals inoculated with the yeast form a more severe, acute infection resulted. In both instances a transitory stimulation of the monocytic cell series followed in either the blood or the omentum and peritoneal fluid, depending on the site of inoculation. In the animals that died during the infection spontaneously, the presence of the yeast organisms could be demonstrated.

In the animals with a generalized infection, skin sensitivity of apparently lasting duration developed within ten to seventy-eight days. The complement fixation test in these animals also became positive after twenty-one days and remained so in the surviving 2 of 5 animals until the experiment was terminated 206 days after inoculation.

SUMARIO

Las Reacciones Celulares e Inmunológicas en los Conejos Infectados con Histoplasma Capsulatum

En los conejos inoculados con la forma micelial del *H. capsulatum* se evocó una infección crónica, generalizada, mientras que en los inoculados con la forma en levadura, sobrevino una infección aguda, más grave. En ambos casos, apareció después una excitación pasajera de la serie de monocitos, ya en la sangre o en el epiplón y líquido peritoneal, conforme al sitio de inoculación. En los animales que fallecieron, pudo distinguirse la presencia de los microbios en levadura.

En los animales con infección generalizada, se produjo cutisensibilidad aparentemente duradera en término de diez a setenta y ocho días. La prueba de fijación del complemento en esos animales también se volvió positiva al cabo de veintiún días, continuando así en los 2 animales que sobrevivieron de 5, hasta que terminó el experimento 206 días después de la inoculación.

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TUBERCULOSIS OF THE HEART

A Review

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INTRODUCTION

Although clinically manifest tuberculosis of the heart is rare, it has been estimated that some degree of involvement of the pericardium, myocardium, or endocardium occurs in approximately 4 per cent of all cases of pulmonary tuberculosis. The occurrence of tuberculosis of the heart is often overlooked because of the similarity between its symptomatology and that of the more apparent pulmonary disease. It is the purpose of this paper to present a review of the literature on tuberculosis of the heart, with reference to the types of lesion encountered and the clinical significance of these lesions.

TUBERCULOSIS OF THE PERICARDIUM (1–32)

Tuberculosis of the pericardium is the most frequent and most important form of tuberculosis of the heart. It occurs in approximately 3 per cent of all cases of tuberculosis. The pericardium is thought to be most commonly invaded by tubercle bacilli by retrograde lymphatic spread from tuberculous mediastinal lymph nodes. Lesions may also arise as a result of hematogenous dissemination of bacilli or, less frequently, by direct extension from the lungs, pleura, or peritoneum. Tuberculous pericarditis is always secondary to tuberculosis elsewhere in the body, and there is no recorded case with satisfactory necropsy studies in which the pericardium was the sole site of involvement. More than 50 cases of tuberculous pericarditis have been reported, which on clinical grounds were considered to be primary. All of these cases which came to autopsy showed tuberculosis of varying extent in other viscera. The highest incidence of cases occurs between the ages of twenty and forty years, and the majority have been in Negroes. The disease has a high mortality rate and its average duration is two to four months. Instances of complete recovery with long periods of follow-up have been reported, more frequently since the advent of streptomycin (30, 32).

Pathology: Any form of pericarditis may occur. It may be fibrinous or fibrocaseous, and most commonly is manifested as pericarditis with effusion. The effusion may be serofibrinous, hemorrhagic, or purulent. The presence of hemorrhagic pericardial effusion favors the diagnosis of tuberculosis provided a malignant tumor of the pericardium can be excluded. Purulent effusion may follow extensive myocardial involvement or, more commonly, direct invasion from caseous mediastinal lymph nodes. Grossly, both layers of the pericardium are covered with a shaggy, thick, fibrinous exudate which closely resembles a simple fibrinous pericarditis. On histologic examination, tuberculous granulation tissue

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is found underlying the layers of fibrin. When the acute pericarditis heals or becomes chronic, the visceral and parietal layers of the pericardium may become loosely adherent. In other cases the entire pericardial cavity becomes obliterated, and the heart is firmly enveloped with fibrous, fibrocaseous, or fibrocalcific tissue. Tubercle bacilli are most numerous in the areas of caseation.

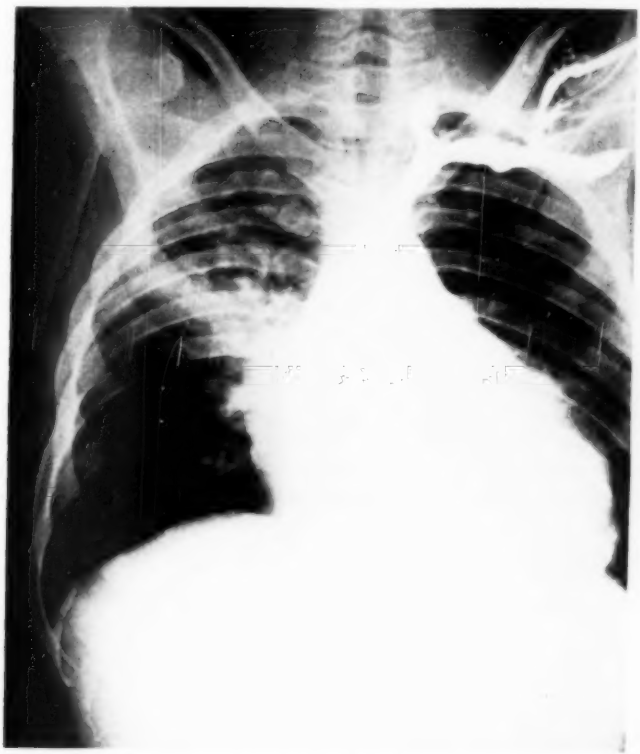

FIG. 1. Frontal angiocardiogram showing the wide space between the opacified right atrium and right heart border making an angiocardiographic diagnosis of pericardial effusion or pericardial thickening.

Symptoms and signs vary with the type and degree of the disease. When active pulmonary tuberculosis is present, the symptoms are often masked. In the so-called primary tuberculous pericarditis the onset is very insidious. There is a long period of lassitude, weakness, low-grade fever, and slight weight loss. Precordial discomfort is not uncommon. A precordial friction rub may be heard for a long period of time during which the patient has few complaints. It has always been surprising to observe how few symptoms these patients have.

Patients in uremia with uremic pericarditis are critically ill. With rheumatic pericarditis the symptoms are more severe and the patients are confined to bed. In acute nonspecific pericarditis, pain is a prominent symptom. As much as 4 liters of fluid may be present in tuberculous pericarditis and, as the pericardial effusion increases, evidence of cardiac embarrassment appears. There is usually progression to terminal congestive heart failure.

Diagnosis: At times the detection of fluid within the pericardium presents some difficulty. Examination has been greatly facilitated, however, by the use of angiocardiography (figure 1). When the films are timed correctly to show right atrial opacification, an increased nonopacified area is also present between the right atrium and the right lung field. Normally this thickness represents the wall of the right atrium and should be no greater than four millimeters on the angiocardiogram. This offers conclusive evidence of pericardial effusion or pericardial thickening. When there is active tuberculosis of the lung or elsewhere in the body, the diagnosis of a concomitant pericarditis due to tuberculosis is relatively easy. The chief difficulty in differential diagnosis is between the so-called clinically primary-type, rheumatic, and uremic pericarditis. Rheumatic pericarditis attacks children and young adults who may show other manifestations of carditis and rheumatic fever. Tuberculous pericarditis usually occurs after the second decade, and is more common in Negroes. Pain is outstanding in rheumatic pericarditis. It is almost entirely absent in tuberculous pericarditis. As a rule, no joints are involved; there are no cardiac murmurs or early development of cardiac failure. The fluid is hemorrhagic, and the presence of tubercle bacilli can often be demonstrated. After aspiration of the fluid and introduction of air, the heart does not appear enlarged on roentgenographic examination. Thickening and calcification of the pericardium may be present. In the acute phase of the disease the mortality is approximately 85 per cent and, in the patients who survive, a chronic illness generally ensues.

Treatment: The pericardial fluid should be aspirated at intervals, and it has been advocated by some that air be introduced (10). This procedure is followed to alleviate cardiac tamponade and to prevent adhesions. When there has been progression to the adherent or constrictive stage, some form of operative procedure may be necessary. An adequate pericardiectomy for surgical correction of the disease should include liberation of all borders of the heart and both venae cavae. Persistence of ascites after pericardiectomy is evidence of an inadequate decortication and demands reoperation and removal of more scar tissue. Cases of acute tuberculous pericarditis which have responded satisfactorily to streptomycin therapy have recently been reported (30, 32).

TUBERCULOSIS OF THE MYOCARDIUM (33–92)

In a careful survey of more than 10,000 autopsied cases of tuberculosis, the incidence of myocardial involvement was 0.28 per cent. The incidence in children alone was 3.9 per cent (71). The first recognized case was reported by Townsend of Dublin in 1832 (33). In cases of tuberculous pericarditis, involvement of the myocardium by direct extension is not unusual but isolated myocarditis is rare.

Proved myocardial tuberculosis without tuberculosis elsewhere in the body has not been reported.

There is no evidence that the nonspecific myocardial fibrosis occasionally seen in patients with tuberculosis is of tuberculous etiology. A diffuse nonspecific myocarditis without typical pathologic changes of tuberculosis and without demonstrable organisms by the Ziehl-Neelsen stain should not be attributed to tuberculosis. It may well be accounted for by one of several other infections or by ischemia incident to disease of the coronary arteries. The mere presence of giant cells with granulation tissue in the myocardium, in the absence of tuberculous lesions in other organs, does not make justifiable a diagnosis of myocarditis of tuberculous origin. No satisfactory explanation exists of the rarity of tuberculosis of muscle, especially cardiac muscle. It has been suggested that the continuous action of the myocardium is a factor preventing multiplication of the tubercle bacilli; this does not seem to impede the multiplication of other bacteria, e.g., *Staphylococci*. The lactic acid produced by muscular activity may offer resistance to the growth of tubercle bacilli. In children, miliary nodules are more frequently seen as compared to the large nodular lesions seen in adults.

Tuberculosis of the myocardium may arise from hematogenous or lymphatic spread or by direct extension. In generalized miliary tuberculosis the hematogenous route is the mode of spread. Caseous tuberculous mediastinal lymph nodes act frequently as the source of involvement of the heart. The bronchial lymph nodes drain the pericardium, and a reversal of lymphatic flow can occur. Direct extension can also occur from these same nodes. They lie closest to the right auricle which for that reason is the area of the heart most often involved. Direct extension from the pleura is also possible. With extensive involvement of the myocardium, rupture of the heart can occur (34–37).

Tuberculosis of the myocardium may occur as a miliary form, a large nodular form, and a diffuse form. The miliary form (38–49) is usually seen in patients with miliary tuberculosis and occurs in less than 10 per cent of the cases. It may be found in any portion of the heart, perhaps more frequently in the right side of the heart. Grossly, small millet-seed–sized, semitransparent, grayish-yellow nodules, one to three millimeters in diameter, are seen. The majority, however, are detectable only on microscopic examination. They may be seen beneath the visceral pericardium and in the papillary muscles. Histologically, the tubercles lie closely to the smaller blood vessels, are situated between the muscle fasciculi, and may be associated with a panarteritis. The tubercles have an appearance similar to those occurring elsewhere in the body. There is a local proliferation of epithelioid cells surrounded by a zone of lymphocytes, with displacement of adjacent muscle fibers and only minimal degenerative changes in the surrounding myocardium. Usually a few giant cells are found. Caseation may occur without much fibrous encapsulation.

The nodular form of tuberculous myocarditis (50–65) is the type of myocardial involvement that has been seen most frequently. The nodules may vary in size from one to seven centimeters in diameter. They may be so large as to completely obstruct one of the cardiac chambers. The nodules are round or oval,

yellowish-gray in color, and are of a firm consistency. Their surfaces are irregularly nodular, and soft areas of caseation and occasionally calcification may be present. The nodules show varying encapsulation, and in places their margins are not sharply demarcated. There is some invasion of the adjacent myocardium. Multiple nodules are not infrequent, for as many as eighteen have been reported in a single heart (66). Involvement of the endocardium with ulceration and thrombosis may occur with miliary dissemination, even in the absence of miliary tuberculosis. With the larger nodules varying degrees of pericarditis are usually present. On histologic examination various stages are observed. At the periphery

FIG. 2. Diffuse infiltrative form of tuberculous myocarditis
(With courtesy and permission of the Journal of Pathology and Bacteriology and J. Thomson)

of one of the nodules, varying degrees of connective tissue are present, with extension into the tuberculoma and into the surrounding interstitial tissues which accounts for the scattered indefinite margins seen on gross examination. The capsule and adjacent myocardium show some lymphocytic infiltration and, as one approaches the areas of caseation, giant cells become generally more abundant. The nodular form of the disease must be differentiated from syphilitic gummata, which can be similar on both gross and microscopic examination. The spirochetal stains and findings in the other viscera aid in the differential diagnosis.

Diffuse tuberculous myocarditis (67 70) is usually seen with tuberculous pericarditis in which the caseation extends directly into the myocardium (figure

2). The extent of myocardial caseation is variable; in some portions of the heart, involvement of the endocardium occurs. Softening may be present in these caseous foci. Grossly, the diseased myocardium is replaced almost entirely by a yellowish-gray, firm material. Associated with this, in the myocardium are found grayish-white strands closely resembling the areas of fibrosis seen in other diseases. At times no apparent changes are visible to the naked eye. On histologic examination the picture varies and often presents diagnostic difficulties. Where caseation is present there are large granular areas where traces of the former myocardium may still be found. Surrounding these areas of caseation is granulation tissue containing giant cells, epithelioid cells, and lymphocytes. Tubercle bacilli are present in large numbers. In the absence of caseation there is an interstitial infiltration of muscle bundles and blood vessels by polymorphonuclear leukocytes, lymphocytes, giant cells, and epithelioid cells. Here there are few tubercle bacilli and, as healing takes place with scar tissue formation, they disappear almost completely. When fibrosis is present alone, the diagnosis of tuberculous myocarditis becomes very difficult. Myocardial changes cannot be considered as tuberculous in origin in the absence of tubercle bacilli, specific histologic changes, and lesions of tuberculosis in other organs (71). Some similarity exists between the interstitial myocardial involvement of tuberculosis and rheumatic fever. They differ in that in active rheumatic myocarditis there is marked parenchymatous degeneration in addition to the interstitial changes. In tuberculosis, despite marked interstitial infiltration, parenchymal involvement is minimal prior to the development of caseation. In tuberculosis of the heart, there is more extensive involvement of the larger coronary arteries than in rheumatic fever.

The diagnosis of tuberculosis of the myocardium is rarely made clinically or even suspected during life due to lack of pathognomonic signs. Palpitation, feeble heart sounds, precordial distress, rapid heart action, gallop rhythm, murmurs, syncope, and congestive heart failure are signs and symptoms encountered. These are clearly not peculiar to tuberculosis of the myocardium. These findings in a young patient, especially a Negro, with known tuberculosis elsewhere are sufficiently suggestive of tuberculosis of the heart to warrant further investigation. When the auricles are involved, auricular fibrillation, auricular flutter, and auricular extrasystoles are common (91–92). In known tuberculous pericarditis, when electrocardiographic changes occur, such as ectopic rhythms, and evidence of myocardial damage appears, the diagnosis should be suspected.

The prognosis in myocardial tuberculosis is always poor and, once congestive failure occurs, the course is rapidly downhill with no response to digitalis expected. The use of streptomycin therapy has been reported (65).

TUBERCULOSIS OF THE ENDOCARDIUM (93–107)

Tuberculous endocarditis, analagous to bacterial or rheumatic endocarditis, is rare. The incidence of this lesion is not known although it has been made the subject of much study. More than 30 cases have been reported as such in the literature (93–106), but these have not all withstood critical analysis and have not

fulfilled the following criteria suggested by Baker (100) to make the pathologic diagnosis: (*1*) The histologic appearance of the endocardial lesions should be similar to tuberculosis occurring elsewhere. (*2*) With appropriate stains one should be able to demonstrate tubercle bacilli. (*3*) Endocardial lesions occurring in a patient with tuberculosis per se are not proof that they are tuberculous in origin. (*4*) It is imperative that all other causes of endocarditis be excluded. No pathogens should be demonstrable. Most of the cases of tuberculous endocarditis have not fulfilled these criteria because of inadequate bacteriologic and pathologic studies.

In generalized miliary tuberculosis, one occasionally sees endocardial tubercles which may occur in any portion of the endocardium including the valves, and may

FIG. 3. An endocardial tubercle on a trabecula of the left ventricle in a case of generalized miliary tuberculosis.

(*With courtesy and permission of the Archives of Pathology and R. Baker*)

vary in size from microscopic lesions to large pedunculated masses. Involvement of the endocardium by spread from a focus in the myocardium or pericardium is not uncommon. These lesions should be called endocardial tuberculosis to distinguish them from true tuberculous endocarditis similar to bacterial endocarditis (figure 3). The rarity of tuberculous endocarditis, in view of the comparative frequency of tuberculous bacillemia, is surprising and is probably due to the very slow growth of the organisms and to small numbers of bacilli being present at one time. True verrucous endocarditis is probably produced by the same mechanism as is thought to operate in rheumatic valvulitis (105). Presumably a tuberculous allergic response occurs with edema of the subendothelial connective tissue and a chronic inflammatory cell infiltration which is aggravated by trauma at the valve-line closure. A row of beaded vegetations then appears, completely covered with endothelium. Later there is deposition of fibrin and platelets. This is rarely seen

at autopsy and may easily be mistaken for a rheumatic process. If by chance during this allergic phase a tuberculous bacillemia should occur, a true verrucous tuberculous endocarditis could develop. The deposited tubercle bacilli are then carried deep into the vegetations by the large mononuclear phagocytes. (Mononuclear phagocytes are not usually present in quantity in normal valves, but appear in large numbers as part of the cellular response in the allergic phase of the valvulitis.)

FIG. 4. Tuberculous endocarditis of the mitral valve
(With courtesy and permission of the Journal of Pathology and Bacteriology and T. Davie)

Pathologic examination grossly shows the involved valves of the heart with pale, yellowish, rounded vegetations forming a fringe along the line of valve closure. They may be several millimeters from the free edge. The vegetations are usually smooth but sometimes are finely roughened not unlike rheumatic vegetations. They are soft and easily detached but not friable. There is usually no adherent thrombus material. Microscopically, the valves show foci of caseation with epithelioid cells, giant cells, and lymphocytes, without involvement of the underlying myocardium. The elastica is intact. Tubercle bacilli are present in large numbers without evidence of other bacteria. The remainder of the myocardium is normal without Aschoff bodies (figure 4).

The differentiation between a true endocardial lesion and a subendocardial

miliary tubercle has given rise to considerable controversy. It has been suggested that the structure of the internal elastic lamella would serve as the best guide for this differentiation.

Cases of tuberculous thrombi in the auricles have been described (96). Tuberculosis in thrombi is due either to invasion of a thrombus from a caseating focus in the myocardium or endocardium or tubercle bacilli deposition in a thrombus already present.

Tuberculosis of the endocardium has been an autopsy finding, the diagnosis not having been made clinically. The symptoms are those usually found with tuberculosis elsewhere, i.e., fever, night sweats, weight loss, and fatigue. In the vegetative endocarditis, the findings may be those of an acute or subacute endocarditis or congestive heart failure The finding of tubercle bacilli in the blood stream does not necessarily confirm the diagnosis. Acute or subacute endocarditis not due to tubercle bacilli may occur in tuberculous patients. The diagnosis, therefore, is always a presumptive one, difficult to make clinically. The prognosis is that of associated disease elsewhere. Healing is said to occur in the vegetative form leading to a certain degree of valvular stenosis (107). The treatment in the active stage is the same as for an active tuberculosis.

SUMMARY

Approximately 4 per cent of patients with tuberculosis at one time or another have cardiac involvement. Except for tuberculous pericarditis, the diagnosis is usually not made clinically. The reason is that the symptoms of pulmonary tuberculosis are similar to, and may mask, any cardiac tuberculosis. The simultaneous presence of any of the other forms of heart disease is usually considered first. Tuberculous involvement of the heart together with the signs, symptoms, pathology, and clinical significance are discussed.

SUMARIO

Tuberculosis Cardíaca

Aproximadamente 4 por ciento de los tuberculosos manifiestan en una ocasión u otra afección cardíaca. Aparte de la pericarditis tuberculosa, no suele hacerse el diagnóstico clínicamente, siendo la causa de ello que los síntomas de la tuberculosis pulmonar son semejantes a los de la cardíaca y pueden enmascarar la última. Primero suele considerarse la presencia simultánea de cualquiera de las otras formas de cardiopatía. Discútense la invasión tuberculosa del corazón, junto con los signos, síntomas, anatomía patológica y significación clínica de los mismos.

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SARCOIDOSIS[1, 2, 3]

Preliminary Report on a Study of 350 Cases with Special Reference to Epidemiology

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INTRODUCTION

During World War II, 350 cases of sarcoidosis were observed in military personnel. The diagnosis was established by histologic examination of material obtained by biopsy of lymph nodes or skin, and the microscopic diagnosis was confirmed in most instances by additional study at the Army Institute of Pathology. A review of the pathology of these cases has been presented by Ricker and Clark (1). We have had the opportunity to study the clinical records of most of these cases and have had access to the records of most follow-up examinations performed by the Veterans Administration, either in hospitals or clinics. To date, we have personally examined 75 of these patients. Only cases in which a histologically proved diagnosis correlated with an acceptable clinical picture of the disease were included for study. At the present time the clinical data are being analyzed and will be reported in detail later.

Many aspects of the clinical picture and etiology of sarcoidosis are not well understood. An evaluation of the life history of sarcoidosis and of the multiplicity of clinical features can be facilitated by the careful long-range study of a large group of cases such as has been made available through the excellent follow-up facilities of the Veterans Administration. A difficult clinical problem is the evaluation of the degree of activity in patients known to have had active disease for a long period of time but now showing little or no evidence of overt abnormalities. Symptomatology has offered little help. A careful correlation of the Kveim reaction, lymph node biopsy, and electrophoretic analysis of plasma proteins has been useful in assessing the presence of disease.

The etiology of sarcoidosis remains obscure. Many competent investigators using precise methods of study have failed to clarify the etiology and, in particular, the relationship to tuberculosis. A unique opportunity has presented itself in the form of a systematic and exhaustive attack on the problem from a combined clinical and epidemiologic standpoint. The epidemiologic studies are being extensively pursued by the Epidemiologic Section of the Division of

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[2] Presented before the Medical Session, as part of the symposium on *Nontuberculous Diseases of the Chest and Related Matters*, at the 46th annual meeting of the National Tuberculosis Association, Washington, D. C., April 26, 1950.

[3] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Infectious Diseases, National Institutes of Health. Although these studies and our own laboratory studies may not uncover an etiologic agent, it is strongly believed that any theories concerning such an agent or agents must take into account the geographical distribution as disclosed in the study herein reported.

EPIDEMIOLOGIC FEATURES

A striking feature noted early in this study was the geographic distribution of cases encountered in this series. This was pointed out by Dr. John C. Ransmeier

FIG. 1. Distribution of cases of sarcoidosis by birthplace. Each dot represents the birthplace of a single patient.

who noted that a sample of cases showed a rather heavy concentration in the southeastern United States. The previously observed predilection of sarcoidosis for the Negro race in this country was also noted in the sample.

The map in figure 1 shows the distribution of patients according to their birthplace. It is obvious that more sarcoid cases detected in the armed forces were born in the southern United States than in any other region. A sample of 226 cases of sarcoidosis in Army personnel, when arranged by birthplace, showed, for both whites and Negroes, a higher proportion of cases in inductees from the South than from other parts of the country (table 1). The similar trend of results in both whites and Negroes suggests a factor other than race alone.

Another interesting feature is that the birthplaces of these patients are predominantly rural. The rural nature of sarcoidosis has been alluded to previously (2). This distribution is particularly striking when closer scrutiny is made of the data from individual states. In Georgia, for example, where no one born in the metropolitan area of Atlanta (with a population of approximately 500,000) developed sarcoidosis, 2 individuals from the rural areas around Lakeland, Georgia (with a population of 1,000) were so diagnosed. Similarly, 2 cases are recorded from Iota, Louisiana, with a population of 1,000. Recently, we have seen a brother and sister who had definite sarcoidosis, and whose mother possibly had it also,

TABLE 1

226 Cases of Sarcoidosis in Army Inductees: Regional Distribution by Birthplace Compared with Army Inductees by Region

REGION*	NUMBER OF INDUCTEES IN THOUSANDS: NOVEMBER 1940 TO OCTOBER 1946	NUMBER OF CASES OF SARCOIDOSIS BY BIRTHPLACE	CASES OF SARCOIDOSIS PER 100,000 INDUCTEES
White			
North	4,676	19	.41
South	1,919	43	2.24
West	790	3	.38
Total	7,385	65	.88
Negro			
North	254	4	1.58
South	633	156	24.63
West	16	1	6.11
Total	903	161	17.81
Grand Total	8,288	226	2.73

* Regions as designated by the national office of vital statistics:
North = New England, Middle Atlantic, East North Central, and West North Central states.
South = South Atlantic, East South Central, and West South Central states.
West = Mountain and Pacific states.

all living on a small farm in northern Georgia. Obviously, not all individuals with sarcoidosis have lived in rural areas, but the interesting feature is that such people outnumber by far those with a predominantly urban residence.

Much can be learned about sarcoidosis by a continued study of these epidemiologic features. Thus far, no common denominator as to animal, vegetable, or industrial contacts has been established in patients interviewed. Although the epidemiologic studies are only in the developmental stage, there are certain possible significances which can be attributed to these preliminary observations.

1. The etiologic agent may be more heavily concentrated in these regions than in other regions of the United States. This, of course, is no new feature for

diseases in general; as an example, one may cite coccidioidomycosis with its definite regional distribution.

2. Individuals from the South may be so constituted or so influenced by their environment that they respond to one or more etiologic agents with the pathologic picture of sarcoidosis. If importance were to be placed on genealogic background, one would expect a high incidence in the upper Midwest because of the heavy Scandinavian population, and in metropolitan areas such as Chicago and Detroit with their heavy Negro population. Such is not the situation in this series. The possibility remains, however, that the same factor in the environment of the endemic area, be it soil, water, foods, or habits, may alter the tissue reactions of the inhabitants to such an extent that the sarcoidosis picture results from an agent that would incite a different disease process away from this locale.

3. The high proportion of individuals with negative tuberculin skin tests may be a factor of epidemiology rather than an actual clinical feature of the disease. A negative tuberculin skin reaction is often listed as a diagnostic feature of sarcoidosis. A positive tuberculin by no means excludes the diagnosis. An analysis of available data in patients of this series reveals a positive tuberculin

TABLE 2

Incidence of Positive Tuberculin Skin Reactions According to Chief Place of Residence

RESIDENCE	NUMBER POSITIVE	NUMBER NEGATIVE	PER CENT POSITIVE
Urban	26	30	46
Rural	25	82	23
Total	51	112	31

skin test in 26, or 46 per cent, of 56 patients who were born in the city or spent the major portion of their lives there (table 2). In contrast, of 107 patients who were born and lived the major portion of their lives in rural areas, only 25, or 23 per cent, had positive tuberculin skin reactions. Thus, it appears that the reported high incidence of negative tuberculin skin reactions may be related to the distribution of the disease predominantly in sections where negative tuberculin skin reactions are commonly encountered, e.g., in rural areas.

4. The apparent higher incidence of sarcoidosis among Negroes in the United States may be related to the regional distribution of the disease.

SUMMARY

Preliminary observations obtained from an analysis of records of 350 patients with sarcoidosis are presented. To date, the most interesting feature noted is the predominance of southern and of rural distribution of birthplaces of these individuals. The implications of these findings are discussed.

SUMARIO

Sarcoidosis: Observaciones Preliminares Derivadas del Análisis de 350 Casos

Estas observaciones preliminares proceden del análisis de los protocolos de

350 enfermos con sarcoidosis. Hasta la fecha, la característica más importante consiste en el predominio meridional y rural en la distribución natal de estos individuos. Discútense las connotaciones de dichos hallazgos.

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BCG VACCINATION IN SARCOIDOSIS[1,2,3]

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INTRODUCTION

An intriguing feature of sarcoidosis is the fact that only one-third of the patients with this disease exhibit a positive tuberculin skin reaction. The percentage of positive reactors to tuberculin among young adults in most parts of this country at this time is no greater than this. In clinic and hospital patients in large eastern cities and in Europe, however, a considerably higher percentage is observed. Since the causative agent of sarcoidosis has not been demonstrated despite intensive study, considerable attention has been given to tuberculin anergy as a clue to the etiology of this disease. The infrequency of positive tuberculin skin reactions in patients with sarcoidosis has been interpreted as evidence both for and against a tuberculous etiology of this disease.

In an effort to evaluate the significance of the tuberculin anergy in sarcoidosis, the response of patients with this disease to artificial inoculation with living avirulent tubercle bacilli (BCG) has been studied. Several possibilities were anticipated. First, that patients with sarcoidosis would develop tuberculin sensitivity in normal fashion, indicating that absence of sensitivity was merely the result of absence of exposure to tuberculous infection. Second, that, if sarcoidosis were of tuberculous etiology, an accelerated or heightened development of sensitivity might be manifested. A third possibility was that patients might fail to develop tuberculin sensitivity, thereby demonstrating a definite immunologic impairment.

Two clinical considerations also appeared to warrant an attempt at BCG vaccination in patients with sarcoidosis. The high incidence of tuberculosis reported to occur among patients with sarcoidosis seemed to justify an attempt to diminish the frequency of superimposed tuberculosis by use of BCG vaccination. A second consideration was the clinical observation that a change of tuberculin skin reaction from negative to positive often accompanied marked improvement of the sarcoid lesions. It seemed possible that, by artificially evoking a positive tuberculin reaction by means of vaccination, clinical improvement might be achieved.

The effect of BCG vaccination in sarcoidosis has been studied by a number of other investigators, and observations have been reported by Lemming (1, 2),

[1] From the Woman's Medical College of Pennsylvania and The Henry Phipps Institute of the University of Pennsylvania.

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[3] Presented before the Medical Session, as part of the symposium on *Nontuberculous Diseases of the Chest and Related Matters*, at the 46th annual meeting of the National Tuberculosis Association, Washington, D. C., April 26, 1950.

Sohier and Gregoire (3), Weissenbach (4), Saenz (5), Leider and Sulzberger (6), and Cornbleet and Rosenthal (7). The results have been variable although, in general, indicate a failure to develop tuberculin sensitivity in normal fashion (table 1). Lemming and Leider and Sulzberger have called attention to the atypical character of the local lesion at the site of vaccination in patients with sarcoidosis, and Cornbleet and Rosenthal have remarked upon the frequency with which clinical improvement occurred following vaccination.

The present report summarizes observations made in 20 patients with sarcoidosis on the response to BCG vaccine and other antigens.

TABLE 1

Reported Observations on Effects of BCG Vaccination in Sarcoidosis

AUTHOR	NUMBER OF CASES VACCINATED	NUMBER DEVELOPING POSITIVE TUBERCULIN	OBSERVATIONS ON INOCULATION LESION	OBSERVATIONS ON CLINICAL COURSE
Lemming, 1937–1942	11	3	Production in some cases of sarcoid-like lesions	—
Weissenbach, 1941	1	0	—	—
Saenz, 1941	1	0	—	—
Sohier et Gregoire, 1945	2	2	—	Remarkable clearing in one case
Leider and Sulzberger, 1949	4	0	Papule formation with absence of ulceration	—
Cornbleet and Rosenthal, 1949	5	1	—	Marked improvement or resolution
Total	24	6		

Procedure of Study

Mention must be made here of the criteria for diagnosis of sarcoidosis, a diagnosis which cannot be established by clinical, roentgenologic, or histologic study alone. It may be defined as a disease characterized by the presence in various tissues of epithelioid cell tubercles with inconspicuous necrosis, often having refractile or apparently calcified bodies in the giant cells of the tubercles. It must be recognized that a similar clinical and histologic appearance has been produced by beryllium granulomatosis, histoplasmosis, tuberculosis, and other diseases. It should be emphasized that the discovery of sarcoid tubercles in excised surgical specimens does not permit a diagnosis of sarcoidosis unless other clinical or roentgenologic evidence demonstrates systemic involvement.

The diagnosis in the patients included in this report has been based on one or more biopsies revealing the characteristic histologic appearance described above. It was considered essential, however, to exclude in each case the principal diseases that may, from clinical and histologic evidence alone, be confused with sarcoidosis. Effort was made to detect beryllium granulomatosis through a detailed occupational and residential history. Evidence of histoplasmosis was sought by use of the histoplasmin skin test, serologic studies, and mycological cultures. Guinea pig inoculation or culture of biopsied material was utilized for the detection of tuberculosis.

A total of 38 patients with sarcoidosis or suspected sarcoidosis have been vaccinated. In the present report, consideration is restricted to 20 patients who met the diagnostic criteria enumerated above, who had been tuberculin negative before vaccination, and in whom serial tuberculin tests were secured after vaccination. All of these patients were Negroes, 4 males and 16 females, ranging in age from fourteen to forty-three years of age. As a control group, similar in race and age but not in sex, a group of tuberculin-negative volunteers were vaccinated. Serial tuberculin tests after vaccination were secured in 29 of these volunteers. Since no sex differences in response to BCG vaccination are known, this appears to be a comparable control group.

BCG vaccine prepared in the laboratories of The Henry Phipps Institute was employed. The vaccine was administered intracutaneously in a standard dose of 0.1 cc., representing approximately 0.1 mg. of various lots of vaccine no older than four days.

Tuberculin skin tests were performed, employing both Purified Protein Derivative (PPD-S) (8) and Old Tuberculin (OT). A first-strength dose of 0.00002 mg. of PPD was used; patients failing to react to this amount were given second-strength tests, using 0.005 mg. of PPD on one arm and 1.0 mg. of OT on the other. Reactions were read and classified in accordance with standard American practice (9). Reactions to second-strength tuberculin, consisting of induration measuring between 5 and 10 mm. in diameter (1 plus reactions), have been regarded as nonspecific and have been considered throughout this report as negative tests. That these reactions are nonspecific and unrelated to tuberculous infection is indicated by the absence of Koch phenomena in the majority of normal persons with such reactions who were given BCG vaccine. No significant discordance has been noted in this study between reactions to PPD and OT.

Tuberculin tests were performed immediately before vaccination, one and two months after vaccination, and thereafter at two- to four-month intervals. Of 9 patients who failed to develop tuberculin sensitivity or who lost their sensitivity following initial vaccination, 5 were revaccinated once, 3 were revaccinated twice, and one was revaccinated three times.

RESULTS

Tuberculin tests following BCG vaccination: In the control group of 29 volunteers, BCG vaccination resulted in the appearance of positive tuberculin skin tests in more than 90 per cent of the subjects. Positive reactions to first-strength tuberculin were noted in 55.2 per cent of the control group.

The skin response to tuberculin of patients with sarcoidosis following vaccination was strikingly different. In none of the 20 cases was a positive reaction to first-strength tuberculin after primary vaccination observed. Positive tests were obtained with second-strength doses in only 9 patients, or 45 per cent. Moreover, as may be seen in figures 1A and 1B, skin sensitivity to tuberculin was poorly maintained in patients with sarcoidosis. In the 9 patients who developed tuberculin sensitivity after primary vaccination, the sensitivity in each instance became negative within ten months.

The response to revaccination may also be observed in figures 1A and 1B. A transitory reaction to first-strength tuberculin was obtained in one patient. Sensitivity to second-strength tuberculin developed slightly, but not significantly, more often after the thirteen revaccinations than after the twenty primary vaccinations, but this sensitivity was as a rule also poorly maintained. Only 15

per cent of the patients remained positive six months after primary vaccination; and 20 per cent of the patients remained positive six months after revaccination. Grouping together the tuberculin tests performed after primary vaccinations and

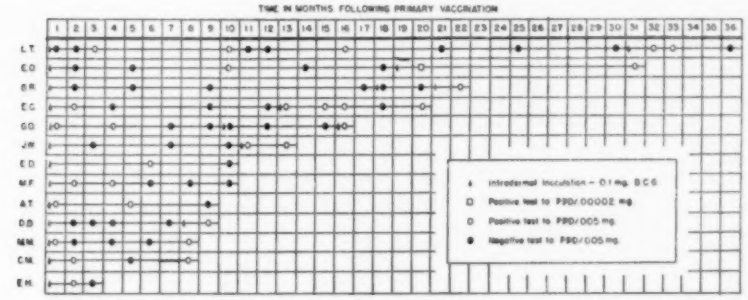
TIME IN MONTHS FOLLOWING PRIMARY VACCINATION
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
L.T.
E.O.
B.R.
E.G.
G.O.
J.W.
E.D.
M.F.
A.T.
D.D.
M.M.
C.M.
E.H.
Intradermal inoculation – 0.1 mg. B.C.G.
Positive test to PPD/.00002 mg.
Positive test to PPD/.005 mg.
Negative test to PPD/.005 mg.

FIG. 1A. BCG vaccination in sarcoidosis. Tuberculin test following primary vaccination

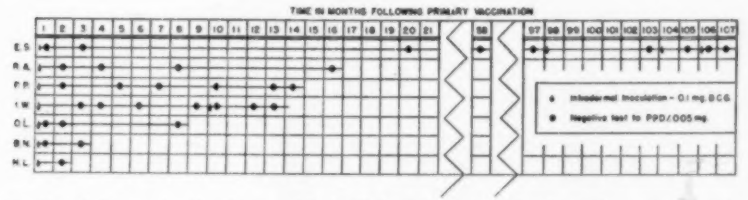
TIME IN MONTHS FOLLOWING PRIMARY VACCINATION
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 58 97 98 99 100 101 102 103 104 105 106 107
E.S.
R.A.
P.P.
I.W.
O.L.
B.N.
H.L.
Intradermal inoculation – 0.1 mg. B.C.G.
Negative test to PPD/.005 mg.

FIG. 1B. BCG vaccination in sarcoidosis. Tuberculin test following primary vaccination

TABLE 2

Frequency of Positive Tuberculin Tests Following BCG Vaccinations in Patients with Sarcoidosis and in Healthy Controls

	TIME IN MONTHS FOLLOWING PRIMARY VACCINATION											
	1		2		3		4 to 6		7 to 12		13 to 97	
	Control	Sarcoid	Control	Sarcoid	Control	Sarcoid	Control	Sarcoid	Control	Sarcoid	Control	Sarcoid
Number of tests	29	15	29	18	—	13	16	22	—	25	—	14
Per cent positive to PPD/.00002 mg.	55.2	0	27.6	5.5	—	0	31.2	0	—	0	—	0
Per cent positive to PPD/.005 mg.	34.5	40.0	72.4	38.9	—	30.8	62.5	22.7	—	24.0	—	14.3
Per cent negative	10.3	60.0	0	55.6	—	69.2	6.3	77.3	—	76.0	—	85.7

revaccinations, the decline in frequency of positive tests with passage of time is evident (table 2, figure 2). The percentage of positive tuberculin reactions obtained declined from 40 per cent at one month and 44.4 per cent at two months to 30.8 per cent at three months, 22.7 per cent at four to six months, and 24 per cent at seven to twelve months. Only 14.3 per cent of tests performed more than

a year after vaccination were positive. In contrast, the skin sensitivity to tuberculin of the vaccinated control group was well maintained at the end of six months.

The tuberculin sensitivity that occurs in approximately one-third of the patients with sarcoidosis as the result of natural infection is apparently more persistent than that observed in this group of experimentally infected patients. One patient, not included in this series, had a negative tuberculin test in November 1946. This was repeated immediately prior to vaccination two months later, and a 3 plus reaction to the second dose was obtained. Although vaccination with BCG was performed, no Koch phenomenon was observed. The patient remained positive to second-strength tuberculin on five subsequent tests performed during the ensuing eighteen months and only became negative on test

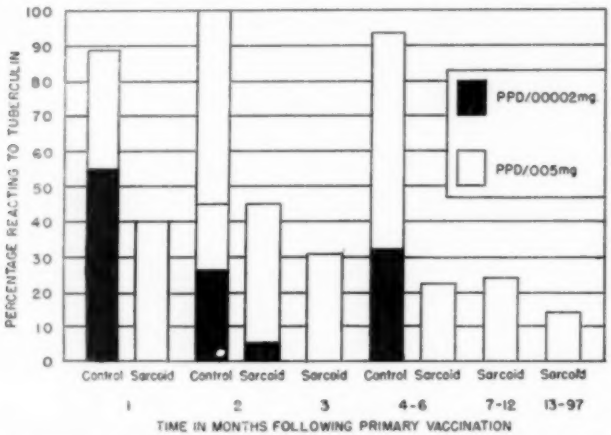

FIG. 2. Frequency of positive tuberculin tests following BCG vaccinations in patients with sarcoidosis and in healthy controls.

twenty-four months later. Our observations on patients with sarcoidosis with positive tuberculin tests indicate that reversion to negative is relatively infrequent as compared to that in vaccinated patients. Although the unvaccinated positive reactors have not been retested quite as frequently as patients in the experimental group, tests at approximately four-month intervals indicate that reversion of the tuberculin test occurs in only a minority of instances observed from one to two years.

Local reaction to BCG vaccination: The vaccinations performed in 29 normal tuberculin-negative controls were followed uniformly within forty-eight to seventy-two hours by the development of a small nodule, 3 to 5 mm. in diameter, at the site of inoculation. About two weeks after vaccination, the development of a papule was noted, and ulceration developed three to eight weeks after vaccination. Healing occurred eight to twelve weeks later, leaving a small residual scar.

In the 20 patients with sarcoidosis, the appearance of the site of vaccination two to three days after primary vaccination was indistinguishable from normal. Ulceration was noted between the third and eighth weeks in 12 patients. In 3 patients ulceration was retarded, and developed between the ninth and sixteenth weeks. In these 15 patients the duration of drainage appeared to be within normal limits, i.e., eight to twelve weeks. In 5 patients ulceration was not detected. Similar observations were made after revaccination; no acute local inflammatory reaction (Koch phenomenon) was observed. Subsequently seven of the ten revaccinations were followed by the development of ulceration within eight weeks, while in one patient three revaccinations failed to provoke ulceration.

No correlation was evident between the development of ulceration and the development or failure of development of skin sensitivity to tuberculin.

Factors influencing the response to BCG vaccination: In an effort to explain the variability in response to tuberculin and in the local reaction to BCG vaccine, the possibility has been considered that the group studied may have comprised

TABLE 3

Occurrence of Ulceration at Site of Inoculation with BCG

	NUMBER OF CASES	0 TO 14 DAYS	3 TO 8 WEEKS	9 TO 16 WEEKS	NO ULCERATION
Controls	29	0	29	0	0
Sarcoidosis					
Initial vaccination	20	0	12	3	5
Revaccination	10	0	7	0	3
Total	30	0	19 (63.3%)	3 (10%)	8 (26.7%)

patients in different clinical stages of sarcoidosis, or even patients with other diseases resembling sarcoidosis. Comparisons have been made of epidemiologic data, clinical findings, and subsequent course of patients who developed skin sensitivity to tuberculin and of those who failed to do so after vaccination with BCG. Similar comparison has been made of patients who exhibited typical local reactions and of those in whom ulceration failed to develop.

The 7 patients who were persistently tuberculin negative after vaccination and the 13 who at one time or another became positive showed no statistically significant differences in sex distribution or age (table 4). Both groups showed the same striking preponderance of patients born in the South Atlantic coastal states from Maryland to Florida. The rarity of native Pennsylvanians in the sarcoid group as compared to their frequency in the control group is noteworthy.

A comparison of certain clinical findings in the 7 tuberculin-negative patients and the 13 tuberculin-positive patients, as shown in table 5, indicates that the former group showed more extensive involvement, especially of the skin, liver, spleen, and eyes. Although these observations suggest that patients with more

extensive and serious involvement were more likely to remain tuberculin negative after vaccination, the differences observed were not significant as determined by the chi-square test, and additional observations will be necessary to determine whether this relationship was due to chance. A similar trend is observable in the data presented in table 6. A benign course was noted somewhat more often in the

TABLE 4

Comparison of Epidemiologic Data in 20 Patients with Sarcoidosis According to Development of Tuberculin Sensitivity after BCG Vaccination

TUBERCULIN TEST	NUMBER OF CASES	SEX		MEAN AGE	BIRTHPLACE		
		M	F	Years	S. Atlantic	Pa.	Other
Persistently negative	7	2	5	26.6	6	0	1
Occasionally positve	13	1	12	28.5	10	1	2
Total sarcoid	20	3	17		16	1	3
Controls	29	29	0	25.6	12	11	6

TABLE 5

Comparison of Clinical Findings in 20 Patients with Sarcoidosis According to Development of Tuberculin Sensitivity after BCG Vaccination

TUBERCULIN TEST	NUMBER OF CASES	THORACIC	PERIPHERAL LYMPH NODES	SKIN	LIVER AND SPLEEN	EYES	BONE	HYPERGLOBULINEMIA
Persistently negative	7	7	7	5	3	2	1	5
Occasionally positive	13	13	11	4	2	1	1	11

TABLE 6

Comparison of Subsequent Course in 20 Patients with Sarcoidosis According to Development of Tuberculin Sensitivity after BCG Vaccination

TUBERCULIN TEST	NUMBER OF CASES	DISAPPEARANCE	IMPROVEMENT	UNCHANGED	PROGRESSION	DEATH
Persistently negative	7	1	3	1	1	1
Occasionally positive	13	3	4	5	—	1

patients who reacted to tuberculin after vaccination, but again the differences in clinical course were slight, and not statistically significant.

Comparisons of these epidemiologic and clinical data in the 15 patients with typical local reactions and the 5 patients whose lesions failed to ulcerate disclosed no significant differences between the two groups.

Response to antigens other than tuberculin: Studies now in progress (11) provide evidence that the depression in immunologic response in sarcoidosis is not confined to tuberculin sensitivity. Immunization with pertussis vaccine of a group

of patients with sarcoidosis has failed to produce normal sensitization as measured by the skin test employing pertussis agglutinogen and by the agglutination titer of serum. If inability to develop tuberculin sensitivity after BCG vaccination occurs in other diseases, and if patients with sarcoidosis respond abnormally to vaccination with other antigens, it seems reasonable to consider that the anomalous response of patients with sarcoidosis to BCG vaccination is not specific but is due to interference with general immunologic mechanisms. Abnormal responses of this type occur in a variety of disseminated granulomatous diseases possibly as a result of diffuse involvement of the reticulo-endothelial system. We have attempted BCG vaccination in a patient with systemic histoplasmosis, and Leider and Sulzberger (6) have described an attempt at BCG vaccination in a boy with a localized granuloma of the chin due to a beryllium-containing foreign body. In both cases tuberculin sensitivity failed to develop.

It is not meant to imply that patients with sarcoidosis are anergic to all agents. Erythema nodosum and eosinophilia, which are generally recognized as manifestations of an allergic state, are not uncommonly observed in sarcoidosis. The patient with histoplasmosis in whom BCG vaccination was performed failed to react to tuberculin on repeated tests before and after immunization, yet exhibited a positive skin test to histoplasmin and a high titer in the colloidal agglutination test for histoplasmosis. Similarly, the anergy which sarcoid patients manifest toward some antigens may be accompanied by, or indeed may be the result of, a powerful response to another antigen. It is altogether possible that application of the proper antigen may elicit a specific allergic response in patients with sarcoidosis.

DISCUSSION

The clinical implications of the use of BCG vaccination in patients with sarcoidosis require only brief discussion. In our experience, the response to BCG vaccination measured either by the tuberculin test or the character of the local reaction is neither sufficiently consistent nor unique to make the procedure of diagnostic value. The response to vaccination is not well enough correlated with the severity and course of the disease to make the procedure a reliable aid in the estimation of prognosis. BCG vaccination does not appear to have significant value as a therapeutic agent. Remission following BCG vaccination was no more frequent than we have observed in unvaccinated patients. Two of the 20 vaccinated patients in this study have died, one of sarcoidosis and the other probably of sarcoidosis. This represents a mortality rate higher than that usually encountered in this disease. It is not possible to state whether BCG vaccination is of value in the prevention of tuberculosis in patients with sarcoidosis. One may be skeptical of the efficacy of this procedure in patients who do not develop and sustain skin sensitivity to tuberculin, but a final judgment can be obtained only by ascertaining the incidence of tuberculosis in a controlled study of large groups of patients with sarcoidosis, a task which will be obviously most difficult of accomplishment.

The principal concern of this investigation has been to ascertain whether a

study of the response to BCG vaccination could clarify the relationship of tuberculosis and sarcoidosis. A majority of Scandinavian investigators and a number in this country have regarded tuberculosis and sarcoidosis as two forms of the same disease, with the anergy observed in sarcoidosis representing an especially high state of immunity in which the tubercle bacilli are destroyed so rapidly by the host that no reaction or only a faint reaction to tuberculin develops.

The fact that patients with sarcoidosis are unable after BCG vaccination to develop and maintain skin sensitivity to tuberculin in normal fashion might appear to support the view that the anergy in this disease is due to a specific relationship with tubercle bacilli. Evidence is available, however, to indicate that the abnormal response to vaccination is not specific, but a general one.

There seems to be no substantial basis for considering the formation of sarcoid-like lesions at the site of BCG vaccination indicative of a specific etiologic relationship of tuberculosis and sarcoidosis. In our experience, the behavior of the gross local lesion in the majority of sarcoid patients is indistinguishable from that observed in controls. The epithelioid, sarcoid-like reactions which have been observed histologically following BCG vaccination (2) are also produced by inoculation of Kveim antigen and extracts of normal splenic tissue (12). This suggests that in sarcoidosis there is a characteristic inflammatory reaction to a number of related or unrelated substances.

It has been demonstrated that a similar tissue reaction may occur as the result of exposure to beryllium fumes or infection with certain mycotic and bacterial organisms. Thus, from the study of local reactions as well as skin sensitivity to tuberculin following BCG vaccination, the changes observed are explicable on the basis of a nonspecific alteration of general immunologic mechanisms produced by causative agents, only a few of which as yet have been identified. The possibility that tubercle bacilli may be one of these causative factors is not excluded by the results of this investigation, but it is difficult in view of the evidence which we have presented to construe anergy to tuberculin as evidence for a tuberculous etiology. The assumption that the tuberculin anergy observed in this disease is specific has been a basic one in the hypothesis that sarcoidosis represents an atypical form of tuberculosis. The demonstration that the anergy is nonspecific thus tends to weaken the case for a tuberculous etiology of this disease. It may safely be concluded that tuberculin anergy does not deserve the emphasis it has received as a clue to the etiology of sarcoidosis.

SUMMARY

A study of BCG vaccination under controlled conditions in 20 patients with sarcoidosis indicates that patients with this disease are unable to develop and maintain skin sensitivity to tuberculin. Atypical local reactions occur at the site of vaccination in a small number of patients with sarcoidosis, but in the majority the local reaction is indistinguishable from normal. Vaccination with BCG does not provide significant assistance to the clinician as a diagnostic or therapeutic agent.

The failure of development of skin sensitivity to tuberculin in patients with sarcoidosis does not establish sarcoidosis as an anergic form of tuberculosis.

The tuberculin anergy exhibited by patients with sarcoidosis appears to be nonspecific, due to interference with general immunologic mechanisms.

SUMARIO

La Vacunación BCG en la Sarcoidosis

Un estudio de la vacunación BCG, bajo condiciones reguladas, en 20 enfermos con sarcoidosis indica que esos enfermos son incapaces de formar y mantener sensibilidad a la tuberculina. En un pequeño número de los enfermos aparecen reacciones atípicas en el sitio de la vacunación, pero en la mayoría la reacción local es indistinguible del estado normal. La vacunación con BCG no aporta mayor ayuda al clínico como agente diagnóstico o terapéutico.

La falta de la aparición de sensibilidad a la tuberculina en los enfermos con sarcoidosis no establece la sarcoidosis como forma anérgica de la tuberculosis. La anergia tuberculínica manifestada por dichos enfermos parece ser anespecífica y debida a intervención con los mecanismos inmunológicos generales.

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IMMUNIZATION STUDIES WITH IRRADIATED TUBERCULOSIS VACCINES[1,2]

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INTRODUCTION

It has now been more than a quarter of a century since Calmette (1) and associates made the announcement that immunity against tuberculosis could be artificially produced by the administration of a viable vaccine prepared from the bacillus of Calmette-Guerin. Although BCG has undergone a stormy struggle for survival, the last few years have witnessed an increased interest and the inauguration of extensive, well-controlled clinical studies. The recent reports of Birkhaug (2), Aronson (3), Rosenthal (4), and other investigators have supplied additional support for the growing application of BCG.

The employment of a live culture vaccine, however, gives rise to several important problems, particularly from the standpoint of its production and distribution. Chief among these is the extremely short life of the culture which makes it virtually impossible to prepare, test for safety and sterility, distribute, and administer within the period of a week. It seems desirable, therefore, to substitute for the classical BCG vaccine one with a longer life which retains its antigenic properties. Modern methods of preservation by drying from the frozen state have been suggested (5) to correct these shortcomings, but it is still too early to assess this modification of BCG vaccine. Since heat-killed and chemically killed whole-cell vaccines have been studied for years without promise, we were prompted to investigate the potentialities of a vaccine prepared from an antigenic virulent human tuberculosis strain inactivated by ultraviolet irradiation.

The attempts of Olson, Habel, and Piggott (6) with the human tubercle bacillus, of Paterson, Crombie, and Coles (7) with the vole bacillus, and our past success in producing vaccines from various pathogenic bacteria and viruses killed by ultraviolet irradiation seemed to justify this approach in the preparation of tuberculosis vaccines.

PREPARATION OF VACCINES

Irradiated vaccines: The test strain was chosen on the premise that a virulent culture of fairly recent isolation might best satisfy the criteria of antigenicity and effectiveness of ultraviolet irradiation, and yet serve as a good challenge organism. The strain chosen for the experimental irradiated vaccine was *M.*

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[2] Presented before the Medical Session, as part of the symposium on *Laboratory and Other Basic Research*, at the 46th annual meeting of the National Tuberculosis Association, Washington, D. C., April 26, 1950.

tuberculosis strain 199RB, a highly virulent human strain from a patient with tuberculosis. It was obtained from the National Institutes of Health. To serve as a companion vaccine for irradiation studies, BCG strain 33 was also included.

Cultures were grown on the surface of Wong-Weinzirl liquid synthetic medium (8) for ten to twelve days, at which time the surface of the medium was covered with a film of actively growing culture. The desired quantity of culture mass was aseptically transferred to a small sterile beaker containing several layers of filter paper. The excess moisture was removed from the culture mass by pressure and then transferred to another beaker for weighing. The culture mass was then transferred to a sterile 100 ml. Pyrex centrifuge bottle containing Pyrex beads, a few drops of saline solution were added, and the bottle was tightly stoppered and mechanically rotated for three hours. The resulting suspension was then further diluted with sterile saline solution, filtered through four thicknesses of sterile nylon, and further diluted to contain 1 mg. semi-moist weight of organisms per ml.

Microscopic examination of the suspensions so prepared showed a large number of single cells, some small aggregates of a few cells each, and a small amount of cellular debris. Immediately following preparation the suspensions were irradiated by the Oppenheimer-Levinson (9) lamp. Because it is desirable to irradiate no longer than necessary for consistent killing of the organisms, careful titration studies were made of irradiation time to determine the shortest exposure period that would consistently produce killed suspensions. After samples had been removed for viability and safety tests, merthiolate was added to the irradiated vaccines in a final concentration of 0.01 per cent.

BCG (comparison) vaccine: The BCG vaccines used in our experiments were prepared by the same procedure from the classical strain 33 except that irradiation and the addition of a preservative were omitted.

Viability tests: Immediately following irradiation, 400 ml. quantities of the irradiated vaccines and control samples of suspensions before irradiation were subjected to high-speed centrifugation; the resulting centrifugates, which contained the concentrated cell mass from 400 ml. of vaccine, were heavily seeded onto glycerine agar and Petragnani's medium and held at 37°C. for four months. Irradiated vaccines have at no time been used for antigenic tests until viability tests were at least one month in progress.

Irradiated vaccines were safety-tested by the intraperitoneal injection of 5 ml. quantities into guinea pigs (300 to 350 gm.) which were then held for six to nine months, after which time they were sacrificed and carefully examined for progressive disease.

RESULTS

Antigenic properties: The initial experiment was planned to ascertain whether there was any evidence that these irradiated vaccines possessed potential antigenic value. Groups of guinea pigs (350 to 400 gm.) were tuberculin tested with 0.005 mg. of PPD and all negative reactors were divided into equal groups. Separate groups received intraperitoneally 5 ml. (5 mg. of organisms) of irradi-

ated tuberculosis vaccine, irradiated BCG, or a fresh 24-hour BCG vaccine weekly for a total of three doses. A group of animals of equal number was set aside as controls.

Three weeks after the last immunizing dose, each animal and a group of normal animals received intraperitoneally 0.1 mg. of a ten- to twelve-day culture of *M. tuberculosis* 199RB of established virulence prepared as for vaccine production but not irradiated. Animals were held four months after challenge. All animals dying during this time were autopsied and examined for the extent of tuberculous infection and possible cause of death. Intercurrent infections were high in this experiment and may have confused the cause of death in some instances. All animals surviving the four-month period were sacrificed, autopsied, and the gross extent of tuberculous infection recorded.

TABLE 1

Four-month Survival Rates of Guinea Pigs Infected with M. tuberculosis Subsequent to Vaccination with Irradiated Tuberculosis Vaccines

ANTIGEN	DOSAGE	CHALLENGE (0.1 MG.)	TUBERCULOSIS DEATHS	SURVIVALS		OLSON *et. al* (6) PER CENT
				Number	Per cent	
Irradiated tuberculosis vaccine, lot 1	5 mg. intraperitoneally each week for three weeks	199RB	6/19	13/19	68	45
BCG	5 mg. intraperitoneally each week for three weeks	199RB	6/15	9/15	60	25
BCG-irradiated, lot 1	5 mg. intraperitoneally each week for three weeks	199RB	14/16	2/16	12	Not given
Controls	None	199RB	34/48	14/48	29	29

This experiment has been evaluated in two ways: (*1*) by the percentage of survivals; and (*2*) by the extent of gross tuberculous infection as measured by an adaptation of the Feldman Index (10).

1. The survival rates are presented in table 1. Of the animals receiving irradiated tuberculosis vaccine and BCG, 68 and 60 per cent were alive four months after challenge, while only 12 per cent of the animals receiving irradiated BCG vaccine and 29 per cent of control animals survived. Compared with the results reported by Olson, Habel, and Piggott (6), our irradiated vaccine and BCG gave higher survival rates than the 45 and 25 per cent survivals which they reported for similar vaccines. This may be due to either the tenfold larger challenge dose (1 mg.) used by Olson or the prolonged irradiation period which they employed.

2. Further evaluation of this experiment has been made by modification of the Feldman Index.

Feldman has reported a scheme for expressing numerically the tuberculous changes in experimentally infected guinea pigs. When applied to gross appearances, the method con-

sists of assigning values to the spleen, liver, lungs, and inoculation site on the basis of extensive, moderate, or minimal tuberculous involvement. This method has been applied to the evaluation of the experiments here reported. Since our animals were infected intraperitoneally instead of subcutaneously as in Feldman's work, we prorated the point value of the infection site to the other organs. In the Feldman Index, the maximal arbitrary theoretical amount of tuberculosis possible in any one animal is considered as 100 units. Table 2 shows the assessed values used in this index.

Evaluation of the test vaccines by this modification of the Feldman Index is given in table 3. The index of the surviving animals in the irradiated tuberculosis vaccine is 40, as compared to 69 for BCG, 89 for BCG-irradiated, and 83 for the controls. As would be expected, there is little difference in the indices of the groups of tuberculous dead.

TABLE 2

Modification of Feldman Index: Theoretical Values of Infection on Organs

ORGAN	VALUE ASSIGNED TO EXTENT OF INFECTION		
	Advanced Tuberculosis	Moderate Tuberculosis	Minimal Tuberculosis
Liver	28	22	11
Spleen	39	22	11
Lungs	33	22	11

Maximal theoretical infection = 100.

TABLE 3

Evaluation of Irradiated Tuberculosis Vaccines on Basis of Feldman Index

ANTIGEN	SURVIVALS	DEATHS	FELDMAN INDEX	
			Survivals	Deaths
Irradiated tuberculosis, vaccine lot 1	13/19	6/19	40	63
BCG	9/15	6/15	69	72
BCG-irradiated lot 1	2/16	14/16	89	69
Controls	14/48	34/48	83	73

Specificity of irradiated vaccine: The apparent protection against infection with the homologous strain shown in the preceding experiment gave rise to the question of whether the antigenicity of the irradiated vaccine was strain specific. An experiment was planned in which a new lot of irradiated vaccine was used for immunization and two strains of *M. tuberculosis*, H37Rv and 199RB, used for challenge. This experiment was designed for termination at a time when definite progressive disease was established in the controls rather than when all or most of the control animals were dead. This method allows, in part, for the difference in character of tuberculous disease in man and in guinea pig, and measures resistance to initial infection rather than the eventual mortality rate. Furthermore, such a procedure helps eliminate the complications so often introduced in long-term experiments by deaths due to intercurrent infections and other causes.

Healthy tuberculin-negative guinea pigs (400 gm.) were immunized as in the preceding experiment with 5 mg. organisms in 5 ml. of new lots of irradiated tuberculosis vaccine, irradiated BCG vaccine, and standard 24-hour BCG vaccine. Vaccines were again given intraperitoneally in three weekly doses.

Four weeks after the last vaccine administration, equal groups of immunized animals along with control groups were given intraperitoneal challenge of 0.01 mg. of *M. tuberculosis* 199RB and H37Rv, prepared as in the previous experiment. Two months later, the animals in the control groups were showing rapid weight loss, and autopsies of randomly sacrificed guinea pigs showed well-established tuberculosis. All animals were then sacrificed and examined to determine the extent of tuberculosis present.

TABLE 4

Evaluation of Irradiated Tuberculosis Vaccines on Basis of Feldman Index

ANTIGEN	NUMBER GUINEA PIGS	DOSAGE	CHALLENGE CULTURE (0.01 MG.)	FELDMAN INDEX*		
				H37Rv	199RB	Average of two challenges
Irradiated tuberculosis vaccine, lot 2	58	5 mg. intraperitoneally each week for three weeks	H37Rv 199RB	29	42	36
BCG	55	5 mg. intraperitoneally each week for three weeks	H37Rv 199RB	32	38	35
BCG-irradiated, lot 2	55	5 mg. intraperitoneally each week for three weeks	H37Rv 199RB	60	76	68
Controls	57	—	H37Rv 199RB	67	79	73

* 100 = Maximal tuberculosis.

A tabulation of the values of the vaccines on the over-all extent of infection is given in table 4. When *M. tuberculosis* H37Rv was used for challenge, the irradiated tuberculosis vaccine gave an index of 29 and BCG an index of 32, as compared with 60 for the irradiated BCG and 67 for the control group. Against a challenge of the homologous strain 199RB, the index for the irradiated tuberculosis vaccine was 42 and BCG was 38, as against 76 for irradiated BCG and 79 for the untreated controls. The values in the last column represent the average indices of the two challenge cultures and are in close agreement with the results of the individual cultures.

In table 5 the autopsy results have been grouped according to the degree of involvement, considering an index of zero as no apparent disease and greater than zero but not greater than 33 as minimal disease. In this experiment, 17

and 13 per cent of the animals receiving irradiated tuberculosis vaccine and BCG, respectively, showed no apparent disease. In contrast, there were no animals in the irradiated BCG and control groups thus classified. Thirty-six and 44 per cent of the irradiated tuberculosis vaccine and BCG animals as against 7 and 5 per cent of the irradiated BCG and control animals showed minimal infection only. In the last column, where these two classifications are combined, 53 and 56 per cent of the irradiated tuberculosis vaccine and BCG groups, as compared with only 7 and 5 per cent of the irradiated BCG and control groups, showed minimal or no tuberculous infection. In these two latter groups, the percentage figures represent minimal infections as there were no animals in the control and irradiated BCG groups that were free of infection.

Comparison of different lots of vaccine: A further experiment was planned to confirm results in previous experiments and to rule out possible wide variations in different lots of vaccines. Tuberculin-negative guinea pigs were immunized

TABLE 5

Irradiated Tuberculosis Vaccines

Degree of Tuberculous Involvement Subsequent to Challenge

ANTIGEN	CHALLENGE CULTURE	NO TUBERCULOSIS FELDMAN INDEX = 0	MINIMAL TUBERCULOSIS FELDMAN INDEX = >0 <33	MINIMAL OR NO TUBERCULOSIS FELDMAN INDEX = <33
Irradiated tuberculosis vaccine, lot II	H37Rv 6/29 199RB 4/29	10/58 (17 per cent)	13/29 8/29 21/58 (36 per cent)	31/58 (53 per cent)
BCG	H37Rv 4/27 199RB 3/28	7/55 (13 per cent)	13/27 11/28 24/55 (44 per cent)	31/55 (56 per cent)
BCG-irradiated, lot II	H37Rv 0/29 199RB 0/26	0/55 (0 per cent)	2/29 2/26 4/55 (7 per cent)	4/55 (7 per cent)
Controls	H37Rv 0/29 199RB 0/28	0/57 (0 per cent)	3/29 0/28 3/57 (5 per cent)	3/57 (5 per cent)

with three 5 mg. semi-moist weight doses of new lots of irradiated tuberculosis and BCG vaccines on the same schedule as was followed in the preceding experiment.

Four weeks after the last dose of vaccine, all animals and a control group were challenged with 0.01 mg. semi-moist weight of an eleven-day culture of *M. tuberculosis* H37Rv. Three months later all animals were sacrificed, autopsied, and examined for the extent of infection.

The over-all degree of infection in terms of the Feldman Index is shown in table 6. The values of 24, 38, and 81 for irradiated tuberculosis vaccine, BCG, and controls, respectively, are in fairly good agreement with the values of 29, 32, and 67 obtained in the previous experiment for the same groups. The control animals in this experiment appear to have somewhat more advanced infections but this might well be explained by the fact that opportunity for the progression of disease was present for an extra month in this group.

The results of this experiment from the degree of tuberculous involvement of

the organs are presented in table 7. Again there was a striking degree of protection, with the irradiated tuberculosis vaccine and BCG apparently protecting 28 and 15 per cent of the animals against gross evidence of infection as compared with no protection in the controls, and 50 and 37 per cent against no more than minimal infection as compared with no animals in the control group. When these two groups are combined, 78 per cent of the irradiated tuberculosis vaccine animals, 52 per cent of the BCG animals, and none of the controls showed minimal or no infection. These results compare favorably with those obtained

TABLE 6

Evaluation of Irradiated Tuberculosis Vaccines on Basis of Feldman Index

ANTIGEN	DOSAGE	CHALLENGE (0.01 MG.)	NUMBER OF GUINEA PIGS	FELDMAN INDEX* AVERAGE
Irradiated tuberculosis vaccine, lot 4	5 mg. intraperitoneally each week for three weeks	H37Rv	28	24
BCG	5 mg. intrapertioneally each week for three weeks	H37Rv	27	38
Controls	—	H37Rv	21	81

* 100 = Maximal tuberculosis.

TABLE 7

Degree of Tuberculous Involvement in Animals Given Irradiated Tuberculosis Vaccines

ANTIGEN	NO TUBERCULOSIS FELDMAN INDEX* = 0	MINIMAL TUBERCULOSIS FELDMAN INDEX >0 <33	MINIMAL OR NO TUBERCULOSIS FELDMAN INDEX <33
Irradiated tuberculosis vaccine, lot 4	8/28 (28 per cent)	14/28 (50 per cent)	22/28 (78 per cent)
BCG	4/27 (15 per cent)	10/27 (37 per cent)	14/27 (52 per cent)
Controls	0/21 (0 per cent)	0/21 (0 per cent)	0/21 (0 per cent)

* 100 = Maximal tuberculosis.

in the previous experiment except that the irradiated tuberculosis vaccine appears somewhat better than in the preceding test.

DISCUSSION

An attempt has been made in the preceding series of experiments to determine the possibility of using ultraviolet irradiation to produce an antigenic tuberculosis vaccine that is nonviable and will possess and retain antigenicity longer than will the classical BCG vaccines. The experiences here reported seem to indicate clearly that the antigenicity of BCG is largely destroyed by short exposure to ultraviolet light. Nevertheless, similar exposure of a virulent human strain such as 199RB appears not to result in the same destruction of the anti-

genic component. This component may exist in different amounts in individual strains. Results of the initial experiment indicated that the irradiated tuberculosis vaccine prepared from the 199RB strain was able to provide protection to guinea pigs at least the equal of that produced by BCG. That survival rates with these vaccines were higher than those reported by Olson may be explainable in view of our present knowledge of the relationship of length of irradiation of vaccines to antigenicity. The considerably longer irradiation period used by Olson may have affected the antigenic value of his vaccine. Also, there well may be considerable differences among the BCG preparations used in these experiments, as wide variations in results with BCG attributed to strain difference and vaccine age are well known. This dependence of antigenicity upon strain may apply also to the selection of strains adaptable for irradiation, and this is being investigated.

Because of the wide differences in the picture of tuberculosis in man and in experimental animals, such factors as susceptibility, mode of infection, progress of the disease, and its prognosis all go together to make the valuation of tuberculosis antigens difficult and empirical. There are only three criteria on which experimental work in animals can be evaluated: mortality, progression of infection, and serological studies. In the first experiment of the series here presented, there is evidence that the mortality is decreased by both BCG and the irradiated tuberculosis vaccine. The overwhelmingly large infectious doses needed for challenge in mortality studies is really an unfair test for an antigen as compared to the estimated smaller inoculum in spontaneous infections in man.

The use of a sublethal challenge in antigenic evaluations is gaining in acceptance and has much to recommend it. Such an infecting dose, followed by artificial termination of the experiment, should give a reliable measure of antigenicity and is especially useful for measuring relative effectiveness of different antigens. The method as used in the foregoing experiments was reproducible with successive lots of vaccines. A summary of experiments employing 301 guinea pigs to which this evaluation was applied is given in table 8. It may be seen that the average values are in accord with those shown in the previous experiments with the irradiated tuberculosis vaccine- and BCG-treated animals showing much less extensive disease.

In table 9 the same series of animals are grouped according to the extent of infection and again more than half of the animals vaccinated with BCG or irradiated tuberculosis vaccine showed no infection or minimal infection.

The method by which we have adapted the Feldman Index to our studies may be open to certain shortcomings. It is true that microscopic lesions may be present and an organ be reported as negative. Macroscopic examination, however, includes the entire organ instead of several isolated sections. It should also be borne in mind that, when all control animals show macroscopically advanced tuberculous lesions, certainly the macroscopic absence of these lesions in vaccinated animals exposed to the same infecting dose should be significant.

No serologic studies have been done on the animals in these experiments. In further studies now in progress, however, attempts are being made to measure

the immune response by the available serologic tests and to correlate the findings with protection studies such as are here reported.

At the present, stability tests on irradiated tuberculosis vaccines are incomplete but we do know that the stability is at least a matter of months rather than of days as with the classical BCG because all irradiated tuberculosis vaccines in this series were more than one month old when used.

TABLE 8

Summary

Value of Irradiated Tuberculosis Vaccines on Basis of Feldman Index

ANTIGEN	DOSAGE	CHALLENGE (0.01 MG.)	NUMBER OF GUINEA PIGS	FELDMAN INDEX* AVERAGE
Irradiated tuberculosis vaccine	5 mg. intraperitoneally each week for three weeks	H37Rv or 199RB	86	32
BCG	5 mg. intraperitoneally each week for three weeks	H37Rv or 199RB	82	36
BCG-irradiated	5 mg. intraperitoneally each week for three weeks	H37Rv or 199RB	55	68
Controls	None	H37Rv or 199RB	78	75

* 100 = Maximal tuberculosis.

TABLE 9

Irradiated Tuberculosis Vaccines—Summary

Degree of Tuberculous Involvement

ANTIGEN	NO TUBERCULOSIS FELDMAN INDEX* = 0	MINIMAL TUBERCULOSIS FELDMAN INDEX = >0,<33	MINIMAL OR NO TUBERCULOSIS FELDMAN INDEX = >33
Irradiated tuberculosis vaccines	18/86: 21 per cent	35/86: 41 per cent	58/86: 62 per cent
BCG	11/82: 14 per cent	34/82: 41 per cent	45/82: 55 per cent
BCG-irradiated	0/55: 0 per cent	4/55: 7 per cent	4/55: 7 per cent
Controls	0/78: 0 per cent	3/78: 4 per cent	3/78: 4 per cent

* 100 = Maximal tuberculosis.

SUMMARY

In successive experiments, vaccines were prepared from a virulent human strain of tubercle bacilli and rendered nonviable by ultraviolet irradiation. These vaccines have shown antigenic values at least equal to BCG on the basis of guinea pig protection tests. More than half of the animals so vaccinated showed no tuberculosis or minimal infection. The stability of these vaccines is at least a matter of months as compared with days for BCG vaccine.

SUMARIO

Estudios de la Inmunización con Vacunas Tuberculosas Irradiadas

En experimentos sucesivos, vacunas preparadas de una cepa humana virulenta del bacilo tuberculoso y aviabilizada con irradiación ultravioleta mostraron valores antigénicos por lo menos iguales a los de BCG a base de pruebas de protección en el cobayo. Más de la mitad de los animales vacunados en esa forma no revelaron ni tuberculosis ni infección mínima. La estabilidad de dichas vacunas es a lo menos cuestión de meses, comparados con días para la vacuna BCG.

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EMOTIONAL FACTORS IN PULMONARY TUBERCULOSIS[1]

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It has long been known that emotional disturbances are capable of altering the physiology or function of a person who is otherwise in good health. Many examples of anxiety states, reactive depressions, and anxiety hysteria occur in everyday practice. Nevertheless, physicians have been slow to accept the concept that the function of a diseased organ can also be altered by emotional stress in such a way that progress towards health may be slowed or reversed. Thus, in each patient there is a dynamic, ever-changing situation in which one must be constantly aware of both the physical status and its influence on mental health, and, in turn, the effect of the emotional state on the patient's disease. The wise physician does not lose sight of either. In institutions where the physician is aware of this interrelationship and acts accordingly, the patients are more easily handled and their progress is more satisfactory.

When a person is first told he has tuberculosis, his first reaction is likely to be one of complete bewilderment. This disease has through the years acquired the reputation in the layman's mind of being synonymous with a condemnation to a short life, gradual wasting away of body, and helpless desuetude while the family is thrown on the mercy of various welfare agencies for the necessities of life. Such terms as "the white plague" and "captain of the men of death" have served to enhance this fear. Today mass roentgenographic surveys have greatly increased the proportion of patients who are suddenly faced with the diagnosis of tuberculosis. Increasingly early discovery of cases has reduced the number of those to whom the warning of failing health gave at least some advance notice in the past.

Many patients are admitted to the tuberculosis sanatorium in a state of great apprehension. When this is added to the new experience of institutional life, the agitation is increased to such a point that many patients demand and obtain their release before the opportunity arises to move them from the admitting ward to permanent quarters. This difficulty is best combated by intelligent and sympathetic supervision by the nurse on duty and by the physician in charge of the case.

Frequently, the many duties imposed upon the doctor do not permit him the time necessary to aid in the adjustment of the patient's emotional problems. In such a situation, the nurses and other personnel employed on the wards are extremely helpful if they are trained to appreciate the fact that pulmonary tuberculosis is a disease of personality as well as of the lungs. It is important to teach the professional help employed at a sanatorium some basic principles of the management of emotional problems. The patient should be urged to "talk his troubles out" to an understanding and sympathetic listener. An explanation

[1] From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

of the true nature of the disease should be given to the patient during this time as well as some concept of the objectives, nature, and duration of treatment. Sedation at night is valuable throughout this period. At times the patient is tractable, but members of the family become agitated and desirous of removing the patient from the institution. A firm attitude should be adopted toward difficult relatives.

The cooperation of the family physician is especially important. The patient who has been given too optimistic an appraisal of his illness in many instances is as difficult a problem as the discouraged patient. Many local physicians tell a patient prior to admission to the sanatorium that the treatment consists essentially of a "few months of bed rest." The patient may interpret this to mean that in a relatively short time he can return to his normal living habits. Such misinformation may be due partly to the physician's lack of knowledge of the nature or extent of the disease. Although the true evaluation may be difficult to accept, it is the most satisfactory basis for a doctor-patient relationship. Several actual experiences reflect most of the various significant psychosomatic problems encountered in patients with tuberculosis.

A 23-year-old white woman was admitted to a tuberculosis sanatorium on Feburary 6, 1948 with a pulmonary lesion of minimal extent. She had been a nurse on the staff of the same institution. On admission her attitude was perhaps best summed up by her own statements: "The whole world just fell on me. Why, the bottom dropped out of everything! I feel like jumping out of the window and never coming back." Over a period of two weeks several conferences were held with her. During these sessions the patient was reassured as to the extent of her disease, and it was impressed upon her that the normal course of events should result in an arrest of the disease. The importance of patience and cooperation on the part of the patient was explained and a plan of therapy outlined. This psychotherapy, together with the judicious use of mild sedation, led to a much better adjustment and acceptance of her disease and its treatment. This patient was discharged from the sanatorium after treatment and is now living at home with her parents in an apparently amicable relationship.

Another trying situation that is all too frequently encountered is that of the patient admitted with far advanced disease, who on occasion may even be *in extremis* on admission. In such a case the relatives often wish to have the patient die at home, and it is with great difficulty they are persuaded that institutional environment is judicious.

A white man, 48 years old, was admitted to a sanatorium on July 8, 1947 with roentgenographic evidence of far advanced bilateral pulmonary tuberculosis. He was *in extremis* on admission. The family was advised of his condition, and expressed the desire to have him at home in his last moments. He was discharged five days later against advice and died in the ambulance on the way home. There were several small children in the home to which this man was being taken.

Another case illustrates rather vividly the dangers involved when such family plans are actually consummated. A 16-year-old Negro girl with far advanced

tuberculosis was expected to die momentarily. Her mother asked to have the patient discharged because of the desire to have her die at home. There had been three previous similar situations in which the same mother had taken an older sister home to die. Because of unhygienic home conditions, each time another child developed pulmonary tuberculosis within a few months. There were still several children at home and the mother was persuaded to allow the girl to remain in the hospital where she died several days later. While in such cases it might be a sympathetic and kindly gesture on the part of the physician to allow the patients to be discharged, personal feelings must of necessity assume a place of secondary importance, if tuberculosis is to be controlled.

When the patient is finally placed on the treatment ward and is settled, the problems encountered are of a different nature. Here many patients who have been in the institution for some time tend to become self-appointed "experts." The old-timers are all too quick to relate their experiences, at times coloring the difficulties to enhance their powers of endurance. This frequently has the desired effect, but it also tends to depress the listener. At times he may become disheartened to the point where he may decide to leave the sanatorium against advice. Hence, visiting among the patients is discouraged when a newcomer is known to have a susceptible disposition.

In many tuberculosis sanatoriums patients are segregated according to economic status; in others, according to the extent of the disease. In most it is a simple procedure reduced to the question of which ward has the first empty bed. There are many arguments in favor of these procedures but, on the premise that emotional status has a definite effect on physical well-being, another element should receive attention. It would be prudent to place the patient in an emotional environment compatible with his personality and conducive to rest and peace of mind. Such character evaluation is useful in choosing roommates and preventing personality clashes.

A white man, 35 years old, was admitted to a sanatorium on June 27, 1948. This patient had moderately advanced bilateral pulmonary tuberculosis. He was of a tense and excitable disposition. Throughout his first four months in the sanatorium he was depressed and decided to leave numerous times. Visits by "boys on the floor" during which they repeated their experiences tended further to depress the patient and to increase his natural apprehension.

A difficulty likely to arise with regularity is the so-called "X-ray pains." In pulmonary tuberculosis a patient's progress is registered by weight gain, the results of sputum examination, and primarily by a chest roentgenogram. Films are usually taken every three months. The patient, because of the anxiety occasioned by this event, frequently develops such symptoms as loss of appetite, inability to sleep well, nervous tension, vague aches and pains, and occasionally an actual weight loss. Prompt reports of roentgenographic findings to the patient serve to control these manifestations of apprehension.

A 45-year-old white man was admitted to the sanatorium on January 22, 1947, with far advanced bilateral pulmonary tuberculosis. Pneumothorax was instituted but proved to be ineffective because of adhesions. One of the follow-up roentgenograms of the chest was taken February 4, 1948. It was several days,

however, before the report was given to the patient. During this time he developed diarrhea, chest pains, and loss of appetite, all of which promptly disappeared when he was told that his progress as shown in the roentgenogram was satisfactory.

Long periods of bed rest are an integral part of any therapeutic program for tuberculosis. During such an experience of enforced idleness, the aches and pains common to everyone are magnified out of proportion to their true significance. The stiffness and soreness occasioned by remaining in one position for a long time become in the mind of the patient evidence of a spread of the disease. The postnasal drip of allergic rhinitis is interpreted as one of the pernicious complications. Reassurance by the physician and practice of the "art of medicine" become the curative agents in such situations.

A white man, 39 years old, was admitted to a sanatorium on April 8, 1947 with bilateral, far advanced pulmonary tuberculosis and with a history of having had a massive pulmonary hemorrhage. The patient had tubercle bacilli in the sputum and was put on strict bed rest. He was tense and emotional. Throughout the first three and a half months of his stay in the sanatorium, he had bilateral chest pains which disappeared completely when he was allowed to get out of bed once a day. During this time he was obsessed with the thought that the chest pains were caused by his disease. Reassurance and a small amount of exercise relieved the pains completely. This patient was discharged from the sanatorium and at last report was working as a clerk for an oil company.

Difficulties in the family of the patient are responsible for many problems. These may vary in their cause from omission of the usual weekly letter to the frequent problem of the socially over active wife or husband. The worry and anxiety caused by such situations are at times responsible for an exacerbation of the disease in many patients and for loss of weight, inability to relax, and similar symptoms. Such circumstances frequently lead to discharge against advice.

The first evidence of pulmonary disease in a 27-year-old white man was in March 1946, at which time he had what was called "flu." Hemoptysis occurred in April 1946, and again in July of the same year. He was admitted to a tuberculosis sanatorium in July 1946 with a diagnosis of far advanced, bilateral pulmonary tuberculosis. Pneumothorax was instituted on the left side and his disease on the right side improved. During April 1947 he was given a leave of absence. At that time his wife threatened divorce. A period of severe anxiety ensued, with loss of appetite, loss of twenty pounds in weight, and the fear that a spontaneous pneumothorax had occurred.

When the patient is judged capable of increasing his activities, the element of impatience becomes manifest. His goal of a discharge is within view and the necessity of proceeding with caution is disregarded. In his anxiety to resume a normal life, he frequently increases his activities too rapidly and the results of such imprudence may cause a relapse. For this reason the discharge of some patients is delayed when it is feared they will be likely to go beyond the limits of endurance imposed by the disease.

A 29-year-old white man was admitted to a sanatorium February 17, 1947

with a diagnosis of far advanced, bilateral pulmonary tuberculosis. The history revealed a previous sanatorium admission in 1941, with discharge against advice. After leaving the sanatorium the first time, the patient worked as a miner. He improved during his first three months in the present sanatorium until he decided that it was unnecessary to remain in bed as much as the physician advised. Roentgenograms of the chest on two occasions revealed progression of the disease, and on one occasion there was no change. Each increase in disease corresponded to a lack of cooperation on the part of the patient.

Following a patient's discharge, two primary problems of a psychic nature remain, the more common being the fear of relapse. Often a patient becomes a psychoneurotic who continually troubles his family physician with inconsequential problems. Too frequently it has been impressed upon patients in the sanatorium that they live by eternal vigilance. The symptoms of a breakdown in tuberculosis are unfortunately simulated by many illnesses such as the cough accompanying the common cold, emotional fatigue, or weight loss secondary to increased physical activity. Realization by the local practitioner of this possibility will save unnecessary cost of laboratory examinations. An explanation of the situation to the patient and sympathetic reassurance may prove of great value in handling such problems. It is possible to prevent many of these unfortunate situations by preparing the patient emotionally for his discharge. This principle is utilized in many institutions through graduated activities. The patient is placed on a program of increasing exercise until he has reached a point at which his exercise tolerance is compatible with the activities which he will be expected to perform in his daily life. Emphasis is given to the fact that he has been living in the sanatorium under supervision on a regimen which is comparable to a normal existence in his home environment. Confidence in his own physical well-being is of inestimable value in preventing later neuroses.

Another problem following discharge is to persuade the patient conscientiously to obtain a chest roentgenogram every three to six months and to be governed by the findings of such films. Negligence may be due to indifference on the part of the patient, or to his desire to put his unfortunate experience as much as possible out of his mind.

A white youth, 18 years old, was first admitted to a sanatorium in August 1946 and discharged in April 1947 to his home where he remained until September 1947. He lost four pounds during the interval at home. The patient was interviewed after roentgenographic evidence of increase in disease was obtained. He stated that while he was at home, he wanted "to have a good time. I didn't have any X-rays and sneaked off to go fishing, swimming, etc."

A survey of the recent literature reveals that an increasing amount of attention is being focused upon the interplay of emotional and physical influences in the patient with pulmonary tuberculosis. Friedman and associates (1) and Thompson and Coulter (2) have pointed out the importance of this relationship. Friedman (1) in a study of 100 patients found that the immediate reaction of the patient upon learning that he had pulmonary tuberculosis varied from unqualified acceptance to an absolute inability to accept such a diagnosis. Twenty-five per

cent of the patients refused to accept the evidence presented. Seventy-nine per cent showed obsessive compulsive characteristics. Friedman advocated that a program aimed at preventing boredom be carried out during hospitalization and at the same time preparing the patient to return to a normal existence following his discharge.

Hartz (3) emphasized the significance of the emotional stress under which the patient existed at the onset of his illness as well as in the atmosphere into which he was placed upon discharge. He states, "In tuberculosis, this is extremely significant, for the balance between being well and being ill is sometimes influenced by subtle factors of strain and fatigue."

It is interesting to note that the earliest reported use of group psychotherapy was not in psychoneurotics but in patients with pulmonary tuberculosis. This form of treatment was instituted by Pratt in Boston in 1905. All authors stress the importance of the physician's approach to the patient and the development of a confidence on the part of the patient in the ability and judgment of the doctor. Discharges against advice in 80 per cent of a group of cases (4) were based upon an emotional or behavior problem. It was suggested that these discharged patients receive aggressive collapse therapy to minimize the chances of contamination.

Basically all of the cases presented reflect the fact that a person rather than an inanimate object had tuberculosis (5). Each patient must be reassured or dealt with in a manner conformable to the situation. The difficulties encountered are a reflection of the individual's background and consequent reactions. Faith in some unseen power or outside agency helps to solve many of the difficulties encountered in a patient under emotional stress. Understanding and proper handling of the psychic problems which confront patients having pulmonary tuberculosis will not only aid in hastening recovery, but will also help to prevent the dissemination of the disease through injudicious acts on the part of the patient or his family.

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THORACOPLASTY FAILURE AS AN INDICATION FOR RESECTION IN PULMONARY TUBERCULOSIS[1]

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INTRODUCTION

There is still controversy as to the criteria for evaluating the results of thoracoplasty. There is especial division of opinion among thoracic surgeons concerning the optimum time which should elapse between the last-stage thoracoplasty and the decision to adopt further procedures because of failure of the thoracoplasty. Actual choice of procedure presents an additional problem. Before pulmonary resection was adopted in the treatment of pulmonary tuberculosis, the choice of operative procedures lay between cavernostomy and revision thoracoplasty. Since the introduction of resection, this procedure has been utilized in many cases of thoracoplasty failure.

Thus, two important problems remain unclarified in cases of thoracoplasty failure: (*1*) When to do "something else," and (*2*) "What to do." The purpose of this paper is to present an analysis of 20 cases of thoracoplasty failure treated with resection in an effort to help clarify these problems.

COMPOSITION OF CLINICAL SERIES

In this series of 20 patients, 18 were female and 2, male. All patients were treated at the Missouri State Sanatorium, Mount Vernon, Missouri, between January 24, 1940 and June 29, 1949. Eighteen patients were white and 2 were Negro. The average age was 34 years, the youngest being 15 and the oldest, 65. The patients had had unsuccessful thoracoplasties from nine months to ten years prior to resection. All patients except one had the modern type of posterolateral, extrapleural thoracoplasty performed in several stages. Only one patient had an anterior-stage thoracoplasty performed. Two patients had revision thoracoplasty done before resection was performed. None of the patients had a cavernostomy before pulmonary resection; 5 had pneumothorax on the contralateral side at the time of resection. Sixteen patients had epidural anesthesia and 4 had nitrous oxide anesthesia. In all, examination of the sputum was positive for acid-fast bacilli before resection.

The following types of resection were done: right pneumonectomy, 7; left pneumonectomy, 5; lobectomy, left lower lobe, 1; lobectomy, right middle lobe and right lower lobe, 2; lobectomy, right upper lobe, 5.

RESULTS

The results in the series of 20 cases of thoracoplasty failure are listed as to mortality, sputum conversion, and postoperative spreads and reactivations (table 1).

[1] From Missouri State Sanatorium, Mount Vernon, Missouri.

Mortality: Six deaths occurred in our series of 20 pulmonary resections for thoracoplasty failure, a mortality of 30 per cent. The causes of death and the time of occurrence were as follows: (*1*) operative death due to generalized toxemia six days postoperatively; (*2*) cerebral embolism occurring twenty hours postoperatively; (*3*) death seventeen days postoperatively from cardiorespiratory insufficiency; (*4*) death seven months postoperatively from toxemia, cardiorespiratory insufficiency, and broncho-pleuro-cutaneous fistula; (*5*) death in shock fifteen minutes postoperatively (This patient had severe cardiac disease.); (*6*) death seven months postoperatively from cardiorespiratory failure.

Sputum conversion: In 12 of the 20 patients in whom sputum examination was positive for acid-fast bacilli prior to resection, conversion to negative occurred. Omitting from consideration the 6 patients who died, the corrected percentage of sputum conversion for the living patients is 85.7 per cent.

Postoperative spreads and reactivations: One instance of postoperative spread occurred three weeks after resection. This patient is still undergoing treatment and has occasional sputum positive for acid-fast bacilli. The patient received nitrous oxide anesthesia instead of the more favorable epidural anesthesia.

TABLE 1

Results in 20 Cases of Pulmonary Resection Performed for Thoracoplasty Failure

Sputum conversion in living patients	85.7 per cent
Total mortality—6 cases	30.0 per cent
Postoperative spread—1 case	5.0 per cent
Postoperative reactivation—1 case	5.0 per cent

In one patient reactivation occurred five months postoperatively. This patient recovered on streptomycin therapy and was discharged as arrested.

CORRELATION OF CLINICAL AND PATHOLOGIC FINDINGS

We have attempted to correlate our three reasons for thoracoplasty failure (residual cavitation, endobronchial tuberculosis, and clinical tuberculous bronchiectasis) with the findings in the surgical specimens. A careful analysis of the 20 chest roentgenograms prior to resection showed that there were 4 patients in whom thoracoplasty failure was due to residual cavitation. In all of these 4 patients, the surgical specimens showed cavitation. There were 5 additional patients, however, who showed cavitation in the surgical specimens but did not show cavitation on chest roentgenogram. It is concluded that a careful roentgenologic study, including laminagrams and "over-exposure" technique, may fail to show the residual cavitation which is the source of the tubercle bacilli found in the sputum in any case of thoracoplasty failure.

Fifteen of the 20 patients with thoracoplasty failure had a bronchoscopic examination between the last stage of their thoracoplasty and their resection. Eleven of the 15 patients showed endobronchial tuberculosis on bronchoscopic examination. Eighteen of the 20 patients showed endobronchial tuberculosis in

their surgical specimens. This divergence is explained as being due to the difficulty in visualizing small bronchi with the bronchoscope.

Seventeen of the 20 thoracoplasty-failure patients had preresection lipiodol bronchograms. Fourteen of the 17 bronchograms showed ectatic bronchi of the division of the lung to be resected. Two patients had almost complete bronchial stenosis of the main bronchus. Examination of the surgical specimens of 18 of the 20 patients revealed bronchiectasis in 18 patients, 2 of whom had the nonspecific type. Therefore, there were 2 patients without complicating endobronchial tuberculosis. The diagnoses on 2 patients with bronchial stenosis visualized by lipiodol bronchograms were confirmed on pathologic examination. Distal to the stenosis, both patients showed tuberculous bronchiectasis which was not revealed by the lipiodol bronchograms. These 2 patients had true tuberculous bronchiectasis, inasmuch as they had stenosis plus dilatation and destruction of the bronchial wall distal to the stenosis.

To summarize the reasons for thoracoplasty failure in the 20 cases under discussion, it was found that 9 patients failed to achieve sputum conversion because of residual cavitation. There were 11 patients in whom the continued finding of acid-fast bacilli in the sputum could be attributed to clinical tuberculous bronchiectasis. One case of thoracoplasty failure was due to a mechanically insufficient thoracoplasty, performed in another institution.

Residual cavitation following thoracoplasty may be the result of selection of unsuitable cases, such as those with giant cavities, thick-walled cavities, and tension cavities. Another cause of residual cavitation following thoracoplasty is a technically inadequate thoracoplasty, which may be due to failure to resect the transverse processes, failure to remove an adequate number of ribs, failure to remove a sufficient length of the ribs, or failure of the patient to lie on the "sand bag" or wear the "shot bag" postoperatively.

Two other conditions which may prevent a successful thoracoplasty are worthy of mention, i.e., a thickened pleura and an indurated lung. The mechanism of residual cavitation following thoracoplasty in the presence of either of these two conditions requires no comment.

Endobronchial tuberculosis may be the source of sputum positive for acid-fast bacilli even after cavity closure and control of the parenchymal disease. An undetermined period of time should be allowed to heal the endobronchial disease before resection is considered, provided that cavity closure is obtained. Endobronchial silver-nitrate cauterization and the use of streptomycin therapy should be followed during the waiting period. If this therapy does not lead to sputum conversion, then resection is indicated.

Endobronchial tuberculosis may cause bronchial stenosis of the ulcerostenotic or the fibrostenotic type. Bronchial stenosis may first be diagnosed following thoracoplasty because a partial stenosis may be converted into a complete stenosis with resulting atelectasis. In our opinion, resection is the treatment of choice in the fibrotic type of bronchial stenosis because bronchoscopic dilatation is often unsuccessful or technically impossible, especially in upper lobe lesions. The ulcerostenotic type of bronchial stenosis should be treated with streptomycin

and cauterization with 30 per cent silver nitrate, as it may heal without stricture formation. If this treatment does not result in healing without stricture formation, resection is indicated, provided the sputum is positive for acid-fast bacilli or the patient has troublesome symptoms as a result of the stenosis. Severe cough with difficulty in releasing retained secretions from dilated bronchi or tuberculous cavities behind the stenosis is considered an indication for resection, especially when the retention of purulent sputum is accompanied by prolonged toxic symptoms.

There is still controversy as to the diagnosis of tuberculous bronchiectasis. In the majority of cases of pulmonary tuberculosis, simultaneous processes of destruction and repair are operative. Either may predominate. The healing process is characterized by irregular interstitial fibrosis and subsequent deformity of the bronchi. If the dilated bronchi are the site of endobronchial tuberculosis, the condition which we propose to call clinical tuberculous bronchiectasis exists. From the standpoint of pathogenesis this is a secondary ectasia with tuberculous implantation.

From the viewpoint of the pathologist, tuberculous bronchiectasis is present only when there is coexisting bronchial stenosis and tuberculous infection behind the stenosis, with resulting destruction of the muscular and elastic layers of the bronchial wall. Thus, only a small proportion of the so-called clinical tuberculous bronchiectasis cases will also be classified pathologically as tuberculous bronchiectasis.

The diagnosis of clinical tuberculous bronchiectasis is made from bronchograms and the finding of acid-fast bacilli in the sputum. The pathologic diagnosis of tuberculous bronchiectasis is made from the surgical specimens.

Differentiation between the two types of bronchiectasis can be made only by pathologic study. Such differentiation, from a practical standpoint, is of minor importance, as both types should be treated the same way. At the present time it is our belief that patients who consistently discharge tubercle bacilli in the sputum and whose bronchograms reveal bronchiectasis should have resection if other sources of the bacilli are excluded. Indeed, primary pulmonary resection has been performed in this hospital in patients in whom clinical tuberculous bronchiectasis was the only indication for the procedure. The location of the bronchiectatic lesion is of importance. If in the lower lobes, it was considered justifiable to perform early resection. In the more common type of upper lobe clinical tuberculous bronchiectasis, better drainage is usually present and pulmonary resection is generally not accepted with this location. It should, however, be considered and, if cavitation cannot be demonstrated by all diagnostic methods, resection is indicated primarily.

Twenty consecutive cases of pulmonary resection performed because of thoracoplasty failure are reviewed and analyzed. Reasons for sputum positive for acid-fast bacilli in a thoracoplasty failure are residual cavitation, endobronchial tuberculosis, and clinical tuberculous bronchiectasis. In the present series of 20 cases there were 9 patients with residual cavitation, 18 patients with endobronchial tuberculosis, and 14 patients with clinical tuberculous bronchiectasis. There

were 11 patients without cavitation and with sputum positive for acid-fast bacilli due only to clinical tuberculous bronchiectasis.

A thoracoplasty failure due to residual cavitation can be treated with revision thoracoplasty, cavernostomy, and pulmonary resection. In our opinion a revision thoracoplasty can be tried first if the failure is not due to clinical tuberculous bronchiectasis or endobronchial tuberculosis. If revision thoracoplasty does not lead to sputum conversion, resection should be done.

When endobronchial tuberculosis is thought to be the source of sputum positive for acid-fast bacilli and all other sources are ruled out, it is recommended that streptomycin and silver-nitrate cauterization be tried before resection is considered. If these methods do not result in sputum conversion, then resection should be done.

When endobronchial tuberculosis is associated with clinical tuberculous bronchiectasis, the writers do not believe in revision thoracoplasty. Instead early resection is advised because it is not believed that bronchiectasis is favorably affected by any form of collapse therapy. When endobronchial disease is complicated by partial or complete bronchial obstruction, pulmonary resection is preferable to revision thoracoplasty.

SUMMARY

An analysis is presented of 20 consecutive cases of thoracoplasty failure in which pulmonary resection was performed. The reasons for thoracoplasty failure are discussed, and a correlation between the clinical findings and the findings on pathologic examination of the surgical specimens are presented. The end results of the operative procedure are listed.

SUMARIO

El Fracaso de la Toracoplastia como Indicación de la Resección en la Tuberculosis Pulmonar

Al analizar 20 casos consecutivos de fracaso de la toracoplastia, se discuten las causas de ese percance y se correlacionan los hallazgos clínicos y anatomopatológicos. Enuméranse los resultados terminales.

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Case Reports

TORSION OF THE SPLEEN ASSOCIATED WITH PNEUMOPERITONEUM[1]

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Torsion of the spleen is not commonly encountered but, if current theories regarding its usual mode of occurrence are correct, it may be seen more frequently in association with the increasing use of pneumoperitoneum. So far as we are able to determine, no previous cases of this type have been reported.

CASE REPORT

The patient was a 26-year-old white woman who became ill following childbirth in August 1948. The diagnosis of pulmonary tuberculosis was made in September, and therapeutic pneumoperitoneum was instituted in December, 1948.

Shortly after the initiation of pneumoperitoneum, the patient began to experience episodes of recurrent, sharp pain in the left upper quadrant, which lasted from one to two hours and disappeared spontaneously. The pain was usually precipitated by the patient's turning on the right side and occurred with greatest frequency just after a pneumoperitoneum refill, although it might occur at any time. For a short time prior to the acute episode to be described, the pain had tended to recur somewhat more frequently. The patient could recall only two previous episodes of abdominal pain. In the first episode, which occurred about ten years earlier, the pain was generalized, and subsided spontaneously. No diagnosis was made. In the second, eight years previously, the pain was in the right lower quadrant, and an appendectomy was performed.

On April 19, 1950, the patient suddenly developed very severe, left upper quadrant pain. Her last pneumoperitoneum refill had been on April 17, 1950. She lay on her right side, with her legs drawn up, but stated that no position gave complete relief from the pain. There was a mass just to the right of the midline below the right costal margin which during the course of the examination shifted to the left side and was then lost to palpation. The mass was subsequently felt without difficulty in the right upper quadrant. It was slightly tender. No muscle spasm or rigidity was evident.

A preoperative diagnosis of torsion of the spleen was made, and the patient was prepared for surgery. Other diagnoses considered were torsion of the omentum or of an intra-abdominal cyst.

The abdomen was opened through a right transverse incision just above the umbilicus over the mass. An enlarged spleen, with at least three clockwise turns on its pedicle, was found beneath the right costal margin. The torsion was first relieved and further exploration carried out. The splenic pedicle was found to be greatly elongated. The gastrosplenic ligament was represented by a thin veil of tissue. No phrenosplenic ligament could be recognized. The pedicle was ligated and the spleen removed. The splenic vein appeared to be thrombosed and a large part of the spleen infarcted.

The pathologist's report was as follows: "The specimen consists of a spleen weighing 330 gm. It measures 15 by 9 by 6 cm. and is slate-blue in color. The capsule is smooth and glistening. At one end there is a thickened wrinkled capsule, and the pulp is white and soft. The microscopic sections of the spleen fail to reveal a specific primary pattern. They do

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show an area of infarction which is surrounded by an adjacent sinusoidal dilatation. The sinusoids generally contain large numbers of leukocytes, whereas the area of infarction is hemorrhagic. The cells lining the sinusoids are prominent due to the sinusoidal distention. There are scattered pigment-laden macrophages present. The splenic capsule is thickened and the mesothelial cells are prominent.

"Diagnosis: Congestion and infarction of the spleen."

DISCUSSION

The symptomatology, diagnosis, and treatment of torsion of the spleen is adequately discussed elsewhere (2). This syndrome is ordinarily a complication of "wandering spleen." The spleen is normally held in a fairly constant position by the gastrosplenic, lienorenal, and phrenocolic ligaments, together with the pressure of other abdominal organs and diaphragm against it. When the ligaments are torn by trauma, stretched by traction, or congenitally lax, abnormal movements of the spleen may take place, especially where the abdominal wall is relaxed and flaccid. A phrenosplenic ligament has been described although it is not usually mentioned in most anatomical texts (1). Certainly the superior portions of the gastrosplenic ligament are also attached to the diaphragm. Wandering spleens are said to be found most frequently in women of middle age whose abdominal wall has been weakened by repeated pregnancies (2). Torsion of the pedicle results from rotation of a "wandering spleen" on its horizontal axis.

Artificial pneumoperitoneum, as used therapeutically for pulmonary tuberculosis, produces ptosis of the abdominal viscera and provides more free space in which the organs may move about. It is suggested, therefore, that wandering spleen and torsion of the spleen may be present much more frequently with pneumoperitoneum than is generally suspected. It is hoped that this report may direct attention to that possibility.

SUMMARY

A case of "wandering spleen" is reported in which torsion of the pedicle occurred in association with artificial pneumoperitoneum. Attention is directed to the possibility that, with the increasing use of pneumoperitoneum, torsion of the spleen may be seen more frequently.

SUMARIO

Torsión Esplénica Asociada a Neumoperitoneo

El caso descrito es de bazo errante, con torsión del pedículo, en asociación con neumoperitoneo terapéutico. Con el creciente empleo del neumoperitoneo, la torsión del bazo tal vez sea observada más frecuentemente.

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TUBERCULOUS MENINGITIS COMPLICATED BY PYOGENIC MENINGITIS CAUSED BY STREPTOCOCCUS FAECALIS[1]

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INTRODUCTION

Cases of tuberculous meningitis complicated by secondary pyogenic meningitis are rare. With the widespread use of intrathecal medication for tuberculous meningitis, such cases will probably occur more frequently. The present case report is that of a child with tuberculous meningitis who in the course of treatment developed a concurrent pyogenic meningitis caused by *Streptococcus faecalis*.

CASE REPORT

M. H., a white female child of ten months, was admitted to Fordham Hospital on December 29, 1948. The child had had an upper respiratory infection for the preceding week and on the morning of admission had a generalized convulsion. The child's mother had active pulmonary tuberculosis and had been hospitalized when the baby was four months old. The child's development had been normal. On November 15, 1948, a chest roentgenogram had been negative. A Mantoux test (0.01 mg. of OT), however, had been positive.

On admission the child was irritable and her temperature was found to be 102.6°F. The pharynx and tonsils appeared moderately inflamed. A careful neurologic examination showed no abnormalities, and it was believed that the child had suffered a febrile convulsion secondary to pharyngitis and tonsillitis. She was given 300,000 units daily of penicillin in aqueous solution in divided doses, but the fever persisted. On December 31 sulfadiazine therapy was instituted. On January 2, 1949, although the pharynx and tonsils were markedly improved, the temperature remained elevated. Penicillin and sulfadiazine were discontinued. On January 3 a left facial palsy was noticed. On January 4 a left hemiparesis involving both the arm and the leg was noted. The pupils were unequal, the left slightly larger than the right, and the pupillary response to light was sluggish. A Mantoux test with 0.001 mg. of OT was positive. The cerebrospinal fluid contained 120 lymphocytes per cu. mm. Chemical determinations gave the following values: sugar, 16 mg. per 100 cc.; chlorides, 720 mg. per 100 cc.; and protein, 30 mg. per 100 cc. Although direct smear was negative for acid-fast bacilli, tubercle bacilli were subsequently recovered from culture of this specimen. One unit of streptomycin per cc. was required to inhibit visible growth of a culture of this organism in Dubos medium for fourteen days, and 10 units of streptomycin per cc. to inhibit for forty-two days. This test was done by the Bureau of Laboratories, Department of Health, New York City.

Streptomycin therapy was begun on January 4 with 1.0 gm. injected intramuscularly daily in divided doses and 50 mg. injected intrathecally daily. The patient also received 2.0 gm. of Promizole daily by mouth. The infant tolerated this therapy fairly well. Little change in her condition was evident for about two weeks. On January 16 vomiting was noted following intrathecal injection, and the frequency of intrathecal medication was reduced to every other day. By January 29 it was noted that the child had better use of her arm. Improvement was very gradual. By February 20 the child had good use of the left arm and left leg. The facial palsy persisted but was less marked. The infant was playful, was feeding well, and could sit up unaided. Her temperature gradually came down after the institution of therapy and remained within normal limits from January 30 to February 28.

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[1] From the Pediatric Service of Fordham Hospital, New York City.

In accordance with the schedule, an intrathecal injection of streptomycin was administered on February 26.

On February 28 the child's temperature suddenly rose to 105°F., and soon thereafter she had a generalized convulsion. No specific signs of meningeal irritation were evident, but the child was very irritable. The leukocyte count was 20,000 per cu. mm., of which 88 per cent were polymorphonuclear leukocytes and 12 per cent were lymphocytes. The cerebrospinal fluid was purulent and contained 550 polymorphonuclear leukocytes per cu. mm. The sugar content was 33 mg. per 100 cc., and the protein, 60 mg. per 100 cc. A smear of the fluid showed many gram-positive cocci, and on culture this organism was identified as *Streptococcus faecalis*. This organism was also recovered from a blood culture taken at this time. Therapy was then instituted with 100,000 units of penicillin intramuscularly every three hours, and 5,000 units of penicillin were injected intrathecally. Oral sulfadiazine therapy was instituted. Since the pyogenic infection had developed while the child was receiving streptomycin and was caused by a strain of *Streptococcus faecalis* resistant to streptomycin *in vitro*, and since the child was already in remission from her tuberculous meningitis, intrathecal streptomycin therapy was discontinued. Intramuscular administration of streptomycin was continued throughout this episode. On this regimen the child's temperature gradually fell and became normal on March 1. The child, however, remained listless and developed nuchal rigidity. On March 3 the infant's temperature again rose to 105°F. The cerebrospinal fluid was purulent and contained 600 polymorphonuclear leukocytes per cu. mm. The sugar content was 31 mg. per 100 cc. and the protein content, 45 mg. per 100 cc. Gram-positive cocci were seen in the smear, and on culture were again identified as *Streptococcus faecalis*. Another intrathecal injection of 5,000 units of penicillin was given and treatment with aureomycin, 250 mg. every six hours by mouth, was started. By March 4 the child's temperature was normal and she appeared markedly improved. Sulfadiazine was discontinued on March 8, penicillin on March 12, and aureomycin on March 13. Cultures of the cerebrospinal fluid examined on March 9 and March 18 yielded no growth. The baby did well until March 26, when her temperature suddenly rose to 104.8°F. Physical examination again showed nuchal rigidity. The cerebrospinal fluid was purulent and contained 1,400 polymorphonuclear leukocytes per cu. mm. A smear showed gram-positive cocci which on culture were again identified as *Streptococcus faecalis*. The child was given one injection of 100,000 units of penicillin intramuscularly and was started on 250 mg. of aureomycin orally every six hours. The infant improved rapidly and the temperature became normal on March 28. Aureomycin was discontinued on April 9. Cultures of specimens of cerebrospinal fluid, obtained on March 28 and April 8, showed no growth.

Studies of the strain of *Streptococcus faecalis* isolated from both cerebrospinal fluid and blood showed that the organism was resistant to 40 units of penicillin per cc. and 5 γ of streptomycin per cc., but was inhibited by aureomycin in a concentration of 0.03 γ per cc. The serum concentration of aureomycin four hours after aureomycin ingestion was 1.9 γ per cc. At the same time the concentration of aureomycin in the cerebrospinal fluid was 0.12 γ per cc.

Following this episode of purulent meningitis, the infant continued to improve. Intrathecal injections of streptomycin were not resumed. By April 29 she was able to sit up easily. Facial weakness was less prominent. By June 19 she was able to walk in her crib and say a few words. On June 4 intramuscular streptomycin therapy was discontinued. The child had received a total of 150 gm. of streptomycin intramuscularly and 1.5 gm. intrathecally. Improvement continued and the child was discharged on October 13, 1949 with only slight residual facial weakness. The cerebrospinal fluid shortly before discharge was within normal limits.

Chest roentgenograms were negative on admission. On February 28 infiltration was noted near the left hilum. On March 16 an area of infiltration was noted in the left upper lobe. This persisted through April and May, but resolution was noted in the early part of June. Roentgenograms taken since this time have been negative. No acid-fast bacilli were found in repeated smears and cultures of gastric aspirates.

Following her discharge the child showed a distinct arrest in development, as exemplified by her failure to learn to walk or talk. Early in February 1950 it was noticed at home that the child was becoming lethargic and, although on February 6 the child suffered a generalized convulsion, her guardian failed to bring her to the hospital as instructed. On February 15 the child had another generalized convulsion, and this time she was readmitted to Fordham Hospital.

On admission, the child was drowsy and irritable, and coarse intermittent aimless movements of the right arm and right leg were noted. Her temperature was 101°F. Her deep reflexes were hyperactive; ankle clonus was present on the right, and a positive Babinski sign was elicited bilaterally. The left leg was slightly shorter than the right. A chest roentgenogram was normal. Examination of the cerebrospinal fluid gave the following values: cells, 170 lymphocytes per cu. mm.; sugar, 12 mg. per 100 cc.; protein, 142 mg. per 100 cc. Numerous acid-fast bacilli were seen in direct smear and *M. tuberculosis* was recovered in cultures of this fluid. One unit of streptomycin per cc. was required to inhibit visible growth of a culture of this organism in Dubos medium for fourteen days.

Intensive therapy was reinstituted. The child received 1.0 gm. of streptomycin daily by the intramuscular route, and 2.0 gm. of Promizole by mouth. Daily intrathecal injections of 50 mg. of streptomycin were given from February 17 to March 5 and from March 7 to March 15, with one last injection on March 18. Despite therapy, the child's condition deteriorated steadily. She became increasingly comatose and it was necessary to feed her by gavage. Her temperature rose gradually so that after March 16 it ranged from 103°F. to 105°F. Generalized convulsions occurred on February 28, March 25, and March 26. Both legs became spastic. Her cerebrospinal fluid showed a gradual increase in sugar content and decrease in protein. Acid-fast bacilli were not seen in smears of the fluid after the first few days of therapy. Streptomycin concentrations in the cerebrospinal fluid ranged from 4.0 to 32 γ per cc. The child's prognosis was considered hopeless, and on March 28 she was transferred to Seton Hospital in poor condition.

DISCUSSION

The occurrence of a complicating pyogenic meningitis due to *Streptococcus faecalis* apparently had no deleterious effect on the immediate course of the tuberculous meningitis in the case detailed above. Although the presence of streptococcal bacteremia leaves open the possibility of infection of the meninges through the blood stream, it is more likely that the organisms were introduced with the intrathecal medication. The scrupulous need for asepsis in intrathecal medication hardly needs amplification.

The course of this complicating infection deserves further consideration. The failure of sustained response to a combination of sulfadiazine, penicillin, and streptomycin is partially explained by the *in vitro* studies cited above which showed resistance of the organism to large amounts of penicillin and streptomycin. The response of the infection to aureomycin can be partially explained by the marked susceptibility of the organism to this antibiotic. It is noteworthy that adequate concentrations of aureomycin in the cerebrospinal fluid were obtained with oral administration of the drug. The relapse, however, needs further explanation. It was thought that the use of penicillin and aureomycin in the first infection might have been less effective than the use of aureomycin alone in the relapse. *In vitro* studies undertaken to clarify this point showed that the presence of penicillin in concentrations of 0.1 unit per cc., 1.0 unit per cc., and 10.0 units per cc. did not alter the susceptibility of this *Streptococcus faecalis* to aureomycin. Penicillin therefore probably did not interfere with the action of aureomycin on this organism *in vivo*.

Meningitis caused by *Streptococcus faecalis* is rare. Giroire, Boquien, and Charbonnel-Moutel (1) in 1945 reported a case in a 41-year-old man following spinal anesthesia. This infection was resistant to sulfonamide therapy but responded to penicillin. In their

review of the literature they found four other cases. One of these died with no specific treatment, one recovered spontaneously, one recovered following intrathecal therapy with an antiserum prepared by means of a specific vaccine, and one recovered on penicillin therapy. Geiger and Greenman (2) reported a case in an adult male successfully treated with penicillin. Long and his associates (3) recently reported the first case of *Streptococcus faecalis* meningitis cured by aureomycin. It is interesting to note that strains of *Streptococcus faecalis* are often susceptible to chloramphenicol (4) and terramycin (5). Although some of the earlier reports were of cases successfully treated with penicillin, in general *Streptococcus faecalis* is relatively resistant to this drug. Aureomycin, chloramphenicol, terramycin, or combinations of these antibiotics, depending on the particular strain of the organism, would appear to offer the most promise of overcoming meningitis caused by *Streptococcus faecalis*.

Cases of tuberculous meningitis complicated by secondary pyogenic meningitis are also rare. Cislaghi (6) in 1940 reported a case of tuberculous meningitis complicated by meningococcal meningitis. In his review of the literature, he found 43 cases of tuberculous meningitis complicated by meningococcal meningitis. Vaden, Rice, and Stadnichenko (7), in a recent review of double meningeal infections in which one of the organisms was the tubercle bacillus, found 3 additional cases associated with meningococcus, and one each with *Klebsiella pneumoniae*, *Diplococcus crassus*, and a *Diplococcus* closely allied to *Gaffkya tetragena*. Csöki (8) reported a case associated with a pneumococcus. Pipers (9), in an earlier review, found 10 cases associated with pneumococcus, *E. coli*, *N. flava*, *G. tetragena*, *H. influenzae*, "pseudomeningococcus," and possible enterococcus. He also found 2 cases of triple meningitis, one involving pneumococcus and *N. catarrhalis;* the other, pneumococcus and meningococcus, in addition to the tubercle bacillus. All of these cases were fatal.

We believe that this is the first case reported of tuberculous meningitis complicated by pyogenic meningitis where the patient recovered from the pyogenic meningitis and had a temporary remission of the tuberculous meningitis.

SUMMARY

A case report is presented of tuberculous meningitis in an infant complicated by a concurrent pyogenic meningitis caused by *Streptococcus faecalis*. The child recovered from the pyogenic meningitis on aureomycin therapy. There was temporary remission of the tuberculous meningitis, but relapse occurred one year later.

SUMARIO

Meningitis Tuberculosa Complicada con Meningitis Piógena Ocasionada por el Streptococcus Faecalis

El caso comunicado es de meningitis tuberculosa en un lactante, complicada por una meningitis piógena concurrente debida a *Streptococcus faecalis*. Con la aureomicinoterapia la niñita se repuso de la meningitis siógena. Hubo también remisión temporal de la meningitis tuberculosa, pero sobrevino una recidiva un año después.

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Editorial

The Philosophy of Abstracting

The world's medical literature has become so voluminous no one person can read and digest it. The same may be said in regard to the literature of some of the specialties. Particularly does this apply to diseases of the chest. In the field of tuberculosis alone, the volume of published material is increasingly great. The *Quarterly Cumulative Index Medicus* devotes more space to the bibliography of tuberculosis than to syphilis, pneumonia, and diseases of the heart combined.

Since the discovery of the antibiotics and their employment in the therapy of tuberculosis, there has been a sharp upsurge of professional and popular interest in this field. This combined interest has resulted in much clinical and laboratory research. Naturally this has stimulated recording and publication, thus materially augmenting the number of printed words to be considered in the search for a few new truths.

Even though the world's literature on tuberculosis could be made available to the average physician, he could not find time to read all of it, or even to search for what he needs from time to time. Neither could the busy specialist in diseases of the chest encompass all that is being written in his special field.

It is obvious that both the general practitioner and the specialist need the help of those who read for the express purpose of sifting, culling, choosing, and epitomizing the pertinent facts for publication. This is an engrossing task, and much time and thought are required to get at the truth and to lay it bare. Placing the kernel of medical knowledge stripped of all superfluous verbiage before the busy physician represents a great service. A ten- to twenty-word abbreviation of an article may clarify and amplify its title and save the busy physician the task of reading ten to twenty pages, or may possibly fix his attention upon the knowledge he seeks. Abstracts should clearly indicate the important subjects under consideration and their interrelationships, noting new procedures, revealed facts, results achieved, and conclusions reached. They should be concise, yet comprehensive and, as far as possible, conclusive. The scope and character of various medical writings necessarily influence the type and length of abstracts. On the other hand, the publications and the purposes for which abstracts are prepared largely determine their attention to detail. For example, the abstracts in THE AMERICAN REVIEW OF TUBERCULOSIS cover articles chosen for a special and, to some extent, limited, group of readers; consequently they are given in greater detail than is possible in *Tuberculosis Index* or the tuberculosis section of *Excerpta Medica*, both of which aspire to world coverage and a much wider reading, with the hope of spotting, alerting, and guiding rather than fully informing. Even so, a careful perusal of the latter publications suggests the desirability of more detail in many instances. Regardless of these conditioning factors, a well-conducted abstract service makes available what Dr.

Samuel Johnson was pleased to call "a smaller quantity containing the virtue of a greater."

In 1899 the American Medical Association first established an abstracting service under the departmental title "Current Medical Literature." In justification of abstracting, this service has been continued under the same title since it was initiated more than fifty years ago. It chooses for abstracting only the more important articles from the general medical literature of the world. In the field of tuberculosis it deals only with those articles having to do with clinical disease. In this country the formidable volumes of chemical abstracts and biological abstracts have taken their place on library shelves, respectively, since 1907 and 1926.

With the growth of medical literature, abstracting has become increasingly important. Many general and special medical periodicals now carry abstracts of current literature within the purview of their respective fields. There are a number of quarterly reviews presenting detailed abstracts in many of the specialties.

THE AMERICAN REVIEW OF TUBERCULOSIS has carried abstracts of important articles on bronchopulmonary conditions since its inception in 1917. No doubt its growing popularity at home and abroad is, in part, due to this service. Its total foreign paid circulation is 2,798. In keeping with the traditions of medical science, it cuts across international lines regardless of foreign policies and feelings. Repeatedly in Editorial Board meetings, the REVIEW's abstract service has been discussed, particularly since other more comprehensive services have become available, but without exception its value was recognized and its continuance recommended. In spite of its limited coverage this policy may be justified by the careful choice of articles and the detailed character of the abstracts.

In an attempt to close all gaps, a number of publications wholly devoted to abstracting in special fields have appeared. Among the latter is *Tuberculosis Index and Abstracts of Current Literature*. This journal is published quarterly in London under the auspices of the National Association for the Prevention of Tuberculosis. It reaches the subscriber's desk in an attractive format, well adapted for ready reference.

Through the services of a research librarian and a local editorial staff of fifty carefully chosen board members and assistants and five overseas correspondents, the world's literature in this special field is carefully scanned for the best, and the results are recorded in abstract. All articles, whether abstracted or not are listed with complete references, making it possible for those who desire fuller information to successfully pursue their studies. The material appears under an appropriate departmental heading with plainly designated supplementary sections, making it readily accessible to the reader. Through such abstracts, wisely employed, the resourceful physician, with a minimum of time and effort, may tap great pools of accumulated knowledge. In *Tuberculosis Index* there is a section on veterinary items and one dealing with medical notes and questions from Parliamentary reports. An appendix, which is usually devoted to some question or problem of special current interest, is also included. The fact that each vol-

ume of *Tuberculosis Index* contains from 700 to 1,000 pages suggests the scope of this publication and the importance of the service it offers.

The tuberculosis section of *Excerpta Medica*, published in Amsterdam, offers a similar service and is comparable in its purpose and its accomplishments. It also is wide in coverage, and has the additional advantage of coordination of abstracts in tuberculosis with abstract sections in general medicine and other specialities.

It is believed that the readers of THE AMERICAN REVIEW OF TUBERCULOSIS and a host of others in need of a more comprehensive knowledge of tuberculosis may want to add one or both of these valuable publications to their available literature on tuberculosis. Certainly they should be in all medical libraries, particularly in those of medical schools, research institutes, and the staff libraries of sanatoriums. It is not possible to know too much about tuberculosis, and it is fatal not to have access to all that is known, at least in abstract.

LEWIS J. MOORMAN

Maxim Steinbach
1892–1930

Maxim Steinbach

1892–1950

On February 1, 1950, the untimely death of Dr. Maxim Steinbach brought to a close a medical career that had been dedicated to the study of tuberculosis for more than thirty years. In the course of that career many significant contributions were made to bacteriology, to clinical medicine, to medical education and, most important of all, to human relationship. It was a career of complete selflessness and all who were associated with any phase of it were deeply enriched by the experience.

Doctor Steinbach was born in New York City on July 21, 1892, attended local schools, and was graduated from the Long Island College of Medicine in 1916. He served a general internship at the Montefiore Hospital in 1917 and continued at that institution in the capacity of House Physician. Dr. Maurice Fishberg was then chief of the Tuberculosis Service and was very much impressed by the young house officer who was so eager to learn and so anxious to help. He invited Doctor Steinbach to join the Tuberculosis Service and the two worked together for many years in a friendship that was broken only by Doctor Fishberg's death in 1935. Their article, "The Diagnosis of Intrathoracic Neoplasms," published in the Medical Record in 1921, was one of the pioneer studies in the differential diagnosis of pulmonary diseases by means of physical signs.

Doctor Steinbach's talents for research were soon apparent, and Doctor Fishberg urged him to undertake a comprehensive study of intestinal tuberculosis to provide basic criteria for its clinical recognition. The results were published in 1930 in THE AMERICAN REVIEW OF TUBERCULOSIS under the title, "Comparative Radiographic and Anatomical Studies of Intestinal Tuberculosis," and the paper was acclaimed at the annual meeting of the National Tuberculosis Association. Doctor Steinbach's career at Montefiore Hospital was a memorable one and he was held in affectionate esteem by his associates, by the administrative staff, and by the board of trustees. He held the position of attending physician for many years and worked untiringly for the welfare and progress of the hospital. His devotion to the ward patients was legendary. Although his private practice was large, he would never let it interfere with his rounds at the city institution or at the country sanatorium. This invariably resulted in maintaining office hours late into the night and left very little personal life for him.

For more than twenty-five years, Doctor Steinbach carried on an active program in the field of experimental tuberculosis at the College of Physicians and Surgeons, Columbia University. He joined the Department of Bacteriology in 1923 and devoted himself to the interests and responsibilities of the Department up to the time of his death. He enjoyed teaching immensely and was loved by his students. His contributions included studies on the mechanisms of resistance to tuberculosis as determined by constitutional factors, endocrine regulation, and vitamin metabolism. Doctor Steinbach also wrote the chapter on tuberculosis

in Dr. Gay's book, *Agents of Disease and Host Resistance*, which was published in 1935. During recent years, his interests were centered on the study of the newer chemotherapeutic and antibiotic compounds. He did considerable experimental research on the sulfonamides, streptomycin, aureomycin, and para-aminosalicylic acid. His most recent study was on *p*-anisaldehyde-thiosemicarbazone.

In a statement made by his associates at Columbia University it was emphasized that Doctor Steinbach was one of those rare physicians who succeeded in combining laboratory work with a busy practice of medicine, and throughout his career maintained a constant correlation between experimentation and clinical knowledge in his specialty. He was a member of the American Medical Association, the New York Academy of Medicine, the New York Academy of Sciences, the Society for Experimental Biology and Medicine, the American Association of Pathologists and Bacteriologists, and Sigma Xi.

As one reminisces over a friendship of twenty years, the past rushes by in a panoramic fashion. The important events recede and the little moments that endeared him so to all of us come into focus. Doctor Steinbach always took his work seriously but never himself. Although not a large man, he was endowed with an unusual amount of physical strength and was apt to demonstrate this prowess at odd moments on an unsuspecting associate. His physical endurance at tennis was another source of great pleasure to him and breath-taking apprehension to his friends. Fortunately his indulgence in this sport occurred only at weekends in the summer.

How shall we mourn one who made our lives so much fuller for having known him; who gave of himself so freely and so graciously and asked for nothing in return. He left us with inspired memories and his family with a glorious inheritance. We shall always think of him in the light of Maclarens' *A Doctor of the Old School*, who served his patients with a devotion that knew no reserve and a kindliness that never failed. He will never be forgotten while one of us lives.

MILTON B. ROSENBLATT

AMERICAN TRUDEAU SOCIETY

Medical Section of the National Tuberculosis Association

Report of the Subcommittee on Pulmonary Function Tests

The Subcommittee on Pulmonary Function Tests held its first meeting in New York on November 17, 1949. All members were present. The Subcommittee attempted to formulate recommendations on pulmonary function tests for tuberculosis hospitals. Their report is as follows:

First, it should be emphasized that much helpful information concerning pulmonary function can be obtained by the simple routine clinical examinations, provided that the observer trains himself to seek out such information from the history, physical examination, and fluoroscopy.

In the history, special attention should be given to diseases or other factors which might alter function of a lobe or of one or both lungs by affecting the thoracic cage, pleura, pulmonary parenchyma, and tracheobronchial tree. Careful inquiry should be made of the patient's reaction to daily activity and to physical stress, both in the past and recently. The importance of such factors as pain, bronchial secretions, and asthma in temporarily reducing lung function must be evaluated. It must also be considered whether the history, especially in relation to dyspnea, is consistent with the clinical observation of, and the results of tests upon, the patient.

In the physical examination, the contour and mobility of the thoracic cage should be noted. The rate and depth of respiration with special attention to prolonged expiration (suggestive of emphysema or partial airway obstruction) or labored breathing at rest is important. The patient should be observed while stripped to the waist after mild exercise (the effect of the specific intensity of such exercise on normal persons must be known to the examiner); the presence of elevated pulse or respiratory rate and the use of the accessory muscles of respiration should be noted. The patient's degree of daily physical activity at the time must be taken into account. This examination must be repeated at the time the patient is being evaluated for collapse or other surgical therapy, and changes from previous observations should be carefully noted.

A fluoroscopic examination is considered an integral part of the physical examination not only to obtain information concerning the intrathoracic lesion but also because it can furnish valuable data on lung function. The examiner's eyes must be *well* accommodated. The patient is first examined during quiet breathing. Attention is directed to the movement of the diaphragm, rib cage, to shift of the mediastinum, whether with inspiration or expiration, and to aeration of the lung fields. Inequalities of pulmonary ventilation should be sought in the two lungs and even in the individual lobes. The cardiocirculatory findings are noted. The patient should be observed during slow and rapid deep inspiration and expiration; the speed and uniformity of lung emptying is to be noted. Failure rapidly to empty the lung or lungs of air may be indicative of partial airway obstruction or of emphysema. If feasible, the fluoroscopic examination may also be repeated in the recumbent position. (Fluoroscopy permits a rough estimate to be made of the relative percentage of ventilation carried on by each lung, but in the occasional case can be in gross error in this regard.)

Chest X-rays should be taken in deep inspiration and also in expiration to record the fluoroscopic findings, but because of their static nature should not replace direct observation of the actual motions under the fluoroscope. The position of the mediastinum

on the inspiratory and expiratory films should be carefully noted. Displacement of the mediastinum toward the opposite side on the expiratory film indicates obstructive emphysema of the lung with the greater degree of radiolucency in expiration. In such cases, the usual X-ray taken only in deep inspiration may fail to give any evidence of obstructive emphysema. The relative position of the leaves of the diaphragm on inspiration and expiration should be compared.

LABORATORY TESTS[1]

Unless a graphic method is used for the registration of the vital capacity, the complemental, reserve, and tidal airs are not usually determined in the average tuberculosis hospital.

Vital Capacity

As customarily performed the vital capacity measures only the quantitative aspect and completely neglects the more important dynamic factors of breathing. Decisions should not be made on the basis of this test. A nearly normal vital capacity may be present in a severe respiratory cripple, and a low vital capacity is no absolute indication of respiratory insufficiency.

The dynamic aspects of the vital capacity determinations are of definite value. A tracing of the vital capacity recorded on a drum revolving at a sufficient speed to portray the rapidity with which air is expelled from the lungs will detect evidence of a partial airway obstruction or trapping of air unless this partial obstruction is localized to one or more lobes of a single lung. Loss of elasticity of the pulmonary parenchyma due to emphysema is shown. This type of measurement is very useful.

When graphic registration of the vital capacity is practiced, the separate graphic determination of the complemental reserve air may give additional information in comparison with the vital capacity. In the presence of bronchospasm or obstructive emphysema the sum of the complemental and reserve air is greater than the volume of the vital capacity. When these three pulmonary volumina are graphically recorded on a fast-moving drum, not only can the prolonged and delayed pulmonary emptying be seen but also the evidence of trapping as illustrated by the difference in the volume of the reserve air as ordinarily determined from the resting expiratory level and the volume of the reserve fraction of the vital capacity breath.

Residual Air

This procedure is of genuine value, especially in cases where the breathing reserves are low and the question of the presence of minor degrees of emphysema or the quantitation of emphysema is important. Complementary air, tidal air, and reserve air are simple measurements of ventilation that can be carried out easily, using a spirometer with a moving drum. At the present time calculation of residual air, however, can be made with accuracy only by a complicated method of gas analysis and should be done in centers where the tests are performed frequently by skilled personnel. The presence and degree of emphysema are most accurately determined by the relative proportion of residual air to the total lung capacity. Our purpose in mentioning the significance of the residual air

[1] The methods of performing the various tests are well described in *Methods of Medical Research*, Yearbook Publishers, Inc., Chicago, 1950. This book contains not only a description of the methods but also gives a well-selected list of references and critical comment. Moreover, it has the advantage of being up-to-date and of bringing together the viewpoints of various individuals

is that all should be aware of its great utility even though it is technically not a simple procedure.

Maximum Breathing Capacity

The determination of the maximum breathing capacity is very valuable. It must be emphasized, however, that the standards for the test will vary slightly in different clinics depending on the manner in which the procedure is conducted. Therefore, it is best for each group to standardize the test on the basis of its method of performance. Depending on the apparatus available, either the graphic (with a recording spirometer) or bag method (measuring the collected air with a meter) may be employed. It is often indicated to perform the test both before and after the administration of bronchodilators.

Exercise Tests

Since the breathing requirements are not the same in different individuals, the response and tolerance of the patient to exercise is a helpful method of evaluating pulmonary function. For this purpose examinations of the type of the step test or the walking ventilation test are available. It is imperative that the responses be interpreted with respect to the intensity of daily activity to which the subject is accustomed at the time of the test.

Bronchospirometry

Bronchospirometry is an important procedure to determine the relative percentage of function of each lung. The total pulmonary function must always be considered in the light of individual lung function. The procedure must be done by a trained team which frequently performs this test if reliable results are to be obtained. Therefore, it is not recommended for the average sanatorium or hospital, but patients requiring this investigation should be sent to special centers. Bronchospirometry is indicated in patients with low maximum breathing capacity in whom the contemplated operative procedure will cause a further reduction. Bronchospirometry is also indicated when a surgical procedure is to be performed on the side of perhaps greater function.

It must be remembered that the percentage of oxygen uptake of the individual lung is of greater importance than its percentage of ventilation.

After the determination of the ventilation and oxygen uptake has been made under resting conditions, it should be repeated for a brief interval with forced breathing in order to bring out partial airway obstruction of unequal degree or present on one side only.

Gas Analyses

Determination of the amount of oxygen or carbon dioxide in the alveolar air and in the arterial and venous blood requires special laboratory facilities and skilled personnel. When simpler studies indicate the need for these determinations, the investigation should be carried out at a qualified center.

MINIMUM REQUIREMENTS

The Subcommittee considers the following to be the minimum requirements in evaluating a patient's pulmonary function:

Careful analysis of the history

Physical examination

A fluoroscopic examination which attempts to evaluate the magnitude, speed, and distribution of pulmonary ventilation

Inspiratory and expiratory chest X-rays

Determination of the maximum breathing capacity

These minimum requirements can be performed in any hospital or sanatorium dealing with diseases of the chest and will yield sufficient information for the management of the great majority of cases. On the basis of these examinations it may be decided whether any additional, more elaborate investigations are necessary before a proper decision concerning surgical or other therapy can be made. Although at present relatively few hospital laboratories are prepared to perform arterial oxygen determinations, it is urged that this procedure be added to the laboratory program in order to permit better recognition of the presence of hypoxia in the patients under treatment by collapse therapy and other methods. By such analyses the indications for oxygen therapy can be better defined.

HERBERT C. MAIER, M.D., *Chairman*
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THE AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

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CLINICAL STUDIES, TUBERCULOSIS

Tuberculoma and Meningitis.—Cerebral tuberculomata vary in size and may be single or multiple. Statistics concerning their incidence are incomplete because few brains are cut in thin slices as advocated by Rich. The most frequent and important mode of infection of the meninges is by way of tuberculomata of the brain substance or of the meninges. In necropsies of 52 cases of tuberculous meningitis, 31 instances of cerebral tuberculomata have been found. Inflammatory reaction is seen in the perivascular spaces near the tuberculomata and in the cortical zones immediately below the meninges. Through these spaces tubercle bacilli could be conducted into the subarachnoid space and this spread would explain the mechanism of secondary or stellate nodules. The presence of perivascular infiltration and tubercle bacilli close to the vessel's lumen suggests that the blood stream might be invaded. Miliary tuberculosis conceivably could originate from such cerebral tuberculomata. Only 19 per cent of adult patients with miliary tuberculosis have simultaneous meningitis and this argues against direct hematogenesis infection as the cause of cerebral tuberculomata. The great frequency of secondary tuberculous meningitis after surgical removal of tuberculous brain tissue is advanced as additional evidence that typical basal exudative meningitis is usually secondary to an intracranial focus and not to simple hematogenous infection.—*Tuberculoma and meningitis, J. Schwarz, Tuberculology, April, 1949, 10: 80.*—(*L. Levin*)

Fever in Tuberculosis.—Eighty-six per cent of cases of tuberculous lobar pneumonia had an acute onset with fever. Lobar involvement of the ulceronodular type was associated with fever in 56 per cent of cases. The excavated infiltrates without lobar involvement had a febrile onset in 25 per cent of cases. Other forms started with fever in 18 per cent of cases.—*Le substratum radiologique des débuts aigus de la tuberculose pulmonaire, H. Brocard & M. Grivaux, Semaine d. hôp. Paris, March 30, 1950, 26: 1093.*—(*V. Leites*)

Epinephrine for Tuberculous Endobronchitis.—Endobronchial ulcerations without pulmonary foci or in the presence of inactive lesions were treated with topical application of epinephrine through the bronchoscope. Over a period of eight years more than 80 per cent favorable results were obtained. If after three or four bronchoscopic treatments no improvement is noted or if worsening occurs, which is considered exceptional, streptomycin and PAS are started.—*Sur le traitement des ulcérations bronchiques tuberculeuses, J. M. Lemoine, Rev. de la tuberc., 1950, 14: 74.*—(*V. Leites*)

Re-expansion after Pneumothorax.—The immediate results of pulmonary re-expansion after 142 therapeutic pneumothoraces show that it is more desirable to discontinue the collapse gradually. Stopping the pneumothorax abruptly may produce high negative pressures with effusion, pleural thickening, and mediastinal shift. In this group of 142 patients, 91 pneumothoraces were discontinued optionally after an average collapse of 64.5 months, more than half of them having been collapsed for longer than 5 years. Full re-expansion was obtained in 44 per cent without appreciable mediastinal shift or evidence of

pleural thickening or effusion. Of the 91 patients 48 had had appreciable effusion during the period of collapse and only 35 per cent of these expanded immediately. Of those without fluid 52 per cent obtained rapid expansion.—*Re-expansion of the artificial pneumothorax lung, T. G. Heaton & W. E. Ogden, Dis. of Chest, March, 1950, 17: 298.*—(*E. A. Rouff*)

Oleothorax in Treatment of Unexpandable Lung.—Over a period of eighteen years, 13 cases of unexpandable lung were treated with oleothorax. Of these, only 3, or 23 per cent, were not benefited by such therapy. Eight patients had had far advanced tuberculosis, while 5 had had moderately advanced disease. The commonest indications for oleothorax have been: (*1*) to disinfect tuberculous empyema; (*2*) to prevent progressive loss of an apparently effective pneumothorax through obliterative pneumothorax; and (*3*) to stiffen an excessively mobile mediastinum. Other uses have been to compress rigid-walled cavities, to treat persistent serous effusions, to treat empyema with mixed infection, and to treat bronchopleural fistula. While the use of oleothorax in the treatment of an unexpandable lung had been mentioned previously, it has not been presented as a definite indication nor have any cases been given. This small group of cases demonstrates the feasibility of using oleothorax in preference to thoracoplasty or prolonged pneumothorax in some cases of unexpandable lung.—*The use of oleothorax for the unexpandable lung, L. C. Evander & J. Lipson, Tuberculology, April, 1949, 10: 65.*—(*L. Levin*)

Unilateral Spinal Tuberculous Abscess.—In case of unilateral paravertebral tuberculous abscess of the thoracic spine the roentgenographic findings were those characteristically found in "dumb-bell" neurofibromas of the spine. The case demonstrated that tuberculosis of the spine can produce a unilateral spinal abscess without bony changes in the associated vertebrae suggesting infection. The posteromesial pleural line was identified in this case and seen not to be displaced. This is unusual in tuberculosis of the thoracic spine, since the common finding is a bilateral paravertebral abscess shadow.—*Unilateral tuberculous abscess of the thoracic spine with roentgen findings of a dumb-bell neurofibroma, J. H. Kneidel, L. A. Smith, & R. E. Bishop, Radiology, January, 1950, 54: 78.*—(*W. J. Steininger*)

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Pituitous Catarrh.—The rare condition of pituitous catarrh was described by Laennec. It is characterized by severe bouts of coughing with expectoration of as much as 1,500 cc. of sputum in twenty-four hours. The sputum is colorless, transparent, ropy, frothy on the surface, and underneath appears like the white of an egg diluted with water. There is some dyspnea. The general condition remains good. There is no toxemia. The condition is chronic and the etiology is unknown. A case is reported in a man aged 36. All efforts at treatment, including antibiotics and anti-allergy measures, were unsuccessful.—*Pituitous catarrh, J. V. Gordon, Lancet, May 27, 1950, 1: 997.*—(*A. G. Cohen*)

Delayed Resolution in Pneumonia.—The major etiologic factors producing delayed resolution in pneumonia were determined in 50 (96.1 per cent) of 52 cases studied. The major process responsible for delayed resolution was found to be impaired bronchial drainage in 22 cases (42.3 per cent); in 4 cases this was the direct result of bronchogenic carcinoma. Other frequent causes of delayed resolution in this group were pulmonary fibrosis and emphysema, arrested pulmonary tuberculosis, chest trauma, chronic bronchitis, and bronchial asthma. A specific organism or chemical insult was responsible for delayed resolution in 16 cases (30.7 per cent). In this category were infections with *Klebsiella pneumoniae*, aspirated anerobic organisms of the oropharynx, *Mycobacterium tuberculosis*, *Streptococcus*, primary atypical pneumonia, and oil aspiration. Intrinsic complications of the pneumonic process, such as lung abscess, lobar or segmental

collapse (atelectasis), pleural effusion, and empyema, caused delayed resolution in 12 cases (23 per cent).—*Major etiological factors producing delayed resolution in pneumonia, T. K. Gleichman, M. M. Leder, & D. W. Zahn, Am. J. Med. Sc., October, 1949, 218: 369.*—(*W. J. Steininger*)

Acute Primary Pulmonary Blastomycosis.—Six cases of primary pulmonary blastomycosis were observed in United States Army personnel on Okinawa. The acute form of the disease was characterized by a prodrome of three to fourteen days; localized chest pain; a productive cough with grayish sputum; an oral temperature of 101° to 102° F.; the absence of superficial lymphadenopathy; the absence of cutaneous lesions; a white cell count of 11,000 to 12,000, with a normal differential; a moderate elevation of the corrected sedimentation rate; and isolation of the organism from the sputum, urine, and possibly the feces. The acute form appeared to be benign as a rule, but could disseminate and lead rapidly to death. There were no specific roentgenographic findings. In this group of cases, 3 showed small, hazy, patchy areas; one presented round-focus lesions; one showed progressive consolidation; and one was manifest only by pleural effusion. In all cases, lymphadenopathy of moderate degree was present either in the hilum or mediastinum. The only conclusion that could be drawn from the roentgenograms of the chest was that the disease was granulomatous and to be considered along with primary tuberculosis, coccidioidomycosis, moniliasis, histoplasmosis, and torulosis. The final diagnosis rested upon laboratory examination of the sputum and urine.—*Acute primary pulmonary blastomycosis, C. P. Bonoff, Radiology, February, 1950, 54: 157.*—(*W. J. Steininger*)

Bronchopulmonary Mycosis.—Four children and their mother developed a mycosis of the lung following a grippe-like onset. Another sibling died of a pneumonic condition at the same time. After a period of inadequate medical care the family was intensively followed over a period of twelve years. Sputum and bronchoscopic specimens were recurrently examined by culture and animal innoculation; skin tests with numerous stock and autogenous antigens were done recurrently; complement fixation and agglutination reactions were obtained; serial blood counts were taken; and chest roentgenograms were made at regular intervals. The etiologic agents were a combination of *Monilia pinoyi* and *Aspergillus niger*. The patients had been exposed to grain and hay-dust, moldy boards, and contaminated chicken feathers in the form of newly-made quilts. The protracted bronchopulmonary symptoms were cleared by the use of massive doses of several types of iodides. Calcification began to replace fibrosis in the lungs about three years after the acute onset, and it had appeared in all 5 individuals at the time of this report. The present state of health is good in all.—*Bronchopulmonary mycosis: Simultaneous primary occurrence in four children and their mother with subsequent diffuse miliary calcification; a twelve year observation, B. M. Hamil, Am. J. Dis. Child., February, 1950, 79: 233.*—(*W. H. Oatway, Jr.*)

Croup in Young Children.—The modern term for croup is "acute laryngotracheobronchitis." It can be very serious. There were 16 deaths in 332 cases; 13 were in infants of less than two and one-half years. The etiology usually is mixed, with two or more of several organisms being present.—*Acute laryngotracheobronchitis, F. C. Emery, Arch. Pediat., March, 1950, 67: 116.*—(*W. H. Oatway, Jr.*)

Status Asthmaticus.—Status asthmaticus frequently is the result of conditions imposed on and by patients who have acute asthma. These patients usually are overmedicated, lack sufficient fluids and food, and oftentimes employ medicaments that check cough and production of secretions. Treatment is carried out in a dust-free hospital room. Fluid intake by mouth and by the intravenous route should be large. Chloral hydrate, sodium bromide, or chlorobutanol is indicated for sedation. Iodine given intravenously as sodium iodide or orally as a saturated solution of potassium iodide is

the best drug for liquefying bronchial secretions. Bronchodilatation should be attempted by the use of aminophylline and caffeine alkaloid. Epinephrine should be used when the patient responds to it but discontinued otherwise. Oxygen alone or mixed with helium will relieve cyanosis. Opiates and atropine must not be used in status asthmaticus. Bronchoscopy for the removal of tenacious mucus has not been necessary since the above outlined plan of treatment was instroduced.—*Status asthmaticus, G. Pines, J. A. M. A., March 18, 1950, 142: 785.—(H. Abeles)*

Wheezing Children.—All is not asthma that wheezes. In an analysis of 151 children from one to eleven years of age, an allergic history, physical examinations, nasal smears, blood counts, etc., were obtained. Fifty-nine were found to be allergic (allergic bronchitis or asthma), and 92 cases (61 per cent) had a nonallergic etiology.—*The "wheezing chest" in children: Review of 151 cases, J. Schwartzman & C. H. Nan, Arch. Pediat., April, 1950, 67: 149.—(W. H. Oatway, Jr.)*

Pulmonary Arteriolosclerosis.—The case reported clinically fulfilled all of the essential diagnostic criteria of Ayerza's disease. Studies of pulmonary function ruled out significant pulmonary emphysema and indicated the presence of a pulmonary lesion, either alveolar or vascular, causing decrease in functioning lung tissue. At necropsy, there were changes in the aorta compatible with syphilis; there was marked hypertrophy of the right ventricle and internal proliferation of the small pulmonary arteries with reduction in their lumen. Similar changes were absent from the small vessels of the greater circulation. This disease occurs most frequently in individuals with syphilis, who in addition have chronic infection of the lower respiratory tract. Because of the lack of more precise knowledge of the etiology of this disease, it is suggested that "Ayerza's syndrome" would be a more proper designation for the clinical picture.—*The etiology of pulmonary arteriolosclerosis (Ayerza's syndrome) with report of an illustrative case, S. S. Leopold, Am. J. Med. Sc., February, 1950, 219: 152.—(W. J. Steininger)*

Pulmonary Nodules.—The chest roentgenogram of a 29-year-old woman with mitral stenosis and insufficiency showed hilar congestion and soft stippling of the lung parenchyma, particularly in the mid-lung fields. The roentgenological examination of the chest of a 45-year-old man with mitral stenosis revealed hilar congestion and numerous calcific areas in the lower two-thirds of both lung fields. The pulmonary nodules found in mitral stenosis are due to a combination of hemosiderosis, fibrosis, chronic congestive changes, engorged vessels, calcification, and ossification. Skin testing may be necessary for differentiating calcifications in mitral stenosis from those due to tuberculosis, histoplasmosis, and coccidioidomycosis.—*Pulmonary nodules associated with mitral stenosis, S. H. Sahn & Ida Levine, Arch. Int. Med., March, 1950, 85: 482.—(G. C. Leiner)*

Siderosis.—Roentgenograms of grinders and burners who worked in a foundry cleaning room were taken annually from 1933 to 1949. Abnormalities were found in 69 cases which included 18.5 per cent of all the workers and 26.8 per cent of all burners and grinders. Others who had exaggerated linear markings were not included in the total. Nodulations developed in 67 per cent of the cases in less than ten years; silicosis usually requires a longer period. The lesions appeared faster among those burners who were exposed to the greatest concentration of iron oxide. The length of time required for appearance of the lesions was in inverse proportion to the concentration of iron oxide in the inspired air. Once the shadows were well established, there was no change even if the individuals continued to work. There were no symptoms and also no deaths and therefore no necropsies. Study of the atmosphere showed insufficient free crystalline silica to produce silicosis. Iron oxide was found in concentrations of 37.4 to 90.0 per cent with an average of 64.3 per cent. It is concluded that siderosis is not a

form of silicosis.—*Siderosis: A benign pneumoconiosis due to the inhalation of iron dust, Part I, L. E. Hamlin & H. J. Weber, Indust. Med. & Surg., April, 1950, 19: 51.—(A. G. Cohen)*

Sarcoidosis.—Among 16 patients with generalized sarcoidosis, the clinical diagnosis was supported histologically in 13; pulmonary involvement was present in 15. These patients were followed for periods ranging from eight months to fifteen years. The earliest intrathoracic lesion was usually hilar lymph node enlargement which generally antedated the pulmonary infiltration. This varied from a micronodular miliary type to a coarse irregular mottling. Either type might clear completely or be replaced by fibrosis consisting most frequently of irregular coarse strands, usually mid-zonal, accompanied by emphysematous changes. A more rare development was a fine reticulated infiltration. Four patients showed gross emphysematous bullae formation. Liver biopsy in 7 patients gave positive results in 5. Of 9 patients treated with calciferol, 3 were completely intolerant of the drug. The remaining 6 showed some degree of improvement, indicating that the effect of calciferol should be investigated further. Among these 16 patients, 6 showed complete recovery with or without calciferol treatment, 7 showed no change, one developed pulmonary tuberculosis, one developed pulmonary tuberculosis and right heart failure, and one showed further increase in the extent of the pulmonary lesions.—*Sarcoidosis, with special reference to the lung changes, J. G. Scadding, Brit. M. J., April 1, 1950, No. 4656: 745.—(E. A. Riley)*

Pulmonary Embolism.—A 57-year-old man received an injection of 600,000 units of penicillin in oil and wax in the course of treatment for syphilis. He noted a peculiar salty taste and a choking pain in the neck immediately after the injection. He also started to cough and became short of breath. On physical examination, four days later, dullness was evident over both lower lobes and moist rales and rhonchi were heard in the same areas. A chest roentgenogram showed irregular areas of decreased illumination in the lower halves of both lung fields. Laboratory examinations revealed 26,200 white blood cells, with an eosinophilia of 62 per cent. A sputum examination was negative for fat droplets. A diagnosis of pulmonary oil embolism was made and the patient was treated with digitoxin, aminophylline, and atropine. He improved within a few days and his chest roentgenogram was normal nineteen days after the injection. —*Pulmonary embolism following injection of penicillin in oil and wax, M. Axelrod, J. A. M. A., March 18, 1950, 142: 802.—(H. Abeles)*

Nitrogen Mustard for Neoplasms.—A series of 210 patients with neoplastic disease received 296 total courses or 1,184 injections of nitrogen mustard. Nitrogen mustard therapy, though only palliative, is most effective in Hodgkin's disease, lymphosarcoma, follicular lymphoblastoma, reticulum cell sarcoma, and mycosis fungoides. In these disease processes nitrogen mustard may be used at any time as long as the leukocyte count is within normal limits. Roentgen therapy is best applied to single localized lesions, saving nitrogen mustard for generalized disease processes. Other conditions which respond fairly well to the drug are fibrosarcoma, leukosarcoma, chondrosarcoma, and monocytic leukemia. Only slight improvement can be expected in melanosarcoma, liposarcoma, and carcinoma, with the possible exception of adenocarcinoma. Nitrogen mustard may be used for symptomatic alleviation in carcinoma, where it may relieve pain; in polycythemia vera, where it may relieve leg cramps due to increased blood viscosity; and in various dermatitides, where it may relieve the itching. Nitrogen mustard has the apparent ability to sensitize to irradiation those patients who have previously become roentgen-ray resistant.—*The clinical effect of nitrogen mustard on neoplastic diseases, R. D. Bauer & L. A. Erf, Am. J. Med. Sc., January, 1950, 219: 16.—(W. J. Steininger)*

Nitrogen Mustard for Bronchiogenic Carcinoma.—Nitrogen mustard was administered

as a palliative measure to 60 patients with inoperable bronchiogenic carcinoma. The dose given was usually 0.1 mg. per kg. repeated on four consecutive days although higher doses were used on a few patients. Sixty-nine per cent of the patients showed moderate to excellent subjective relief of the symptoms of cough, wheeze, dyspnea, and chest pain. Fifty-four per cent of the patients showed objective evidence of improvement. Palliation was greatest in patients with undifferentiated tumors and least in those with well-differentiated epidermoid carcinomas. All relief was temporary and there was no evidence that the lives of the patients were prolonged. Toxic reactions consisting of gastrointestinal disturbances and lymphatic and bone marrow depression were encountered with no fatal results. Gastrointestinal disturbances appeared to be unrelated to the dosage and no relationship to clinical therapeutic results was noted. A fall in the white blood cell count was definitely related to dosage, and it occurred more commonly in patients who showed clinical improvement.—*Nitrogen mustard in the treatment of inoperable bronchiogenic carcinoma. J. P. Lynch, P. F. Ware, & E. A. Gaensler, Surgery, March, 1950, 27: 368.*—(*M. G. Carter*)

Bronchogenic Carcinoma.—A cytologic diagnosis of carcinoma was made in more than 400 cases during the examination of sputum and bronchial secretions from about 6,000 patients. Four-fifths of the diagnoses were made from sputum examination, the remainder being made from direct swabbings of the bronchial wall. There were 2 per cent false positives compared to 30 per cent false negatives. One hundred forty-four cases were explored, 79 (55 per cent) having had a preoperative microscopic diagnosis of carcinoma by bronchial biopsy, while positive smears furnished evidence of malignancy in the remainder. Pneumonectomy or lobectomy was performed on 77 patients, 45 of these being on the basis of positive biopsies and 32 on the basis of positive smears. In 8 of these cases there was little or no communication between the peripherally placed tumor and the bronchial tree; none had given a positive cytologic diagnosis. No diagnoses of bronchial adenoma or cylindroma were made by cytologic examination.—*Cytologic diagnosis of bronchogenic carcinoma, L. B. Woolner & J. R. McDonald, Dis. of Chest, January, 1950, 17: 1.*—(*E. A. Rouff*)

Carcinoma of the Lung.—In a series of 502 patients with carcinoma of the lung, there were almost 6 men to one woman. The majority were from 40 to 60 years of age. Cough was the chief symptom in 71 per cent of the patients, hemoptysis being present in 63 per cent, pain in 50 per cent, marked loss of weight in 39 per cent, shortness of breath in 23 per cent, pneumonitis in 18 per cent and fever in 13 per cent. Roentgenograms were positive in all 502 cases with bronchoscopy being next in importance as an aid to diagnosis. At the time of exploration 344 patients were found to be inoperable. Total pneumonectomy was performed in 158 patients of whom 41 died within less than a month, a total operative mortality of 26 per cent. Fifty-four who are still alive have survived from one month to sixteen years while the remaining 63, who are now dead, survived the operation from a month to six years. The author does not feel that anything short of pneumonectomy is indicated in carcinoma of the lung.—*Clinical analysis and follow-up of 502 cases of carcinoma of the lung, W. F. Reinhoff, Dis. of Chest, January, 1950, 1: 33.*—(*E. A. Rouff*)

Primary Muscle Tumors in the Lung.—Of 7 histologically proved myogenic tumors primary in the lung, 4 were myomas and 3 myosarcomas. Whether benign or malignant, muscle tumors of the bronchial tree show roentgenologically a homogeneous, essentially spherical mass of water density with clear distinct edges. The tumors are single, are usually free in the lung, and average 6 cm. in diameter. They show bronchial displacement with narrowing, and infrequently they may be entirely intraluminal. Both benign and malignant forms may reveal enlargement

over a period of six to twelve months, and there is no way of dependably distinguishing between the two unless there is distant metastasis. Chief among the conditions resembling myogenic lung tumors are certain cases of bronchogenic carcinoma of nodular form, single carcinoma or sarcoma metastases, bronchial adenoma, tuberculoma, hamartoma, and cysts. While an unequivocal diagnosis of myogenic lung tumor is not possible roentgenologically, the diagnosis is to be considered when a certain shadow pattern is encountered in the chest film.—*A roentgen study of muscle tumors primary in the lung, R. S. Sherman & B. H. Malone, Radiology, April, 1950, 54: 507.*—*(W. J. Steininger)*

Hamartoma of the Lung.—Pulmonary hamartoma usually occurs as a solitary, discrete, lobulated, solid mass, often containing calcific areas, situated in the parenchyma near the pleura, and surrounded by apparently normal lung. Cartilage, primitive connective tissue, and islands of glandular tissue are the usual constituents, with fat, bone, smooth muscle, lymphoid tissue, and amorphous calcification occurring less frequently. Hamartoma must be differentiated from bronchogenic carcinoma, solitary metastasis, bronchial adenoma, tuberculoma, and echinococcic cyst. Roentgenographic findings are: (*1*) a sharply defined, parenchymal tumor surrounded by clear lung; (*2*) lobulation of the margins in most cases; (*3*) a peripheral or subpleural location in most cases; (*4*) irregular patches of calcification in many cases; (*5*) areas of lesser density near the periphery of the tumor, occasionally due to collections of fat. Of 3 cases discovered on routine chest examination and proved by surgery, one was diagnosed roentgenographically with the aid of laminagrams (Authors' summary).—*Hamartoma of the lung, E. A. Bragg, Jr. & G. Levene, Radiology, February, 1950, 54: 227.*—*(W. J. Steininger)*

Hemangioma of the Lung.—A case of cavernous hemangioma was recognized after the lesion had been diagnosed as tuberculosis with 2 positive sputum reports. There was no pulmonary murmur, but the case was otherwise typical. A successful lobectomy showed the arteriovenous fistula, but no evidence of tuberculosis.—*Cavernous hemangioma of the lung, J. H. Forsee, H. W. Mahon, & L. A. James, Ann. Surg., March, 1950, 131: 418.*—*(W. H. Oatway, Jr.)*

Pleural Carcinosis.—A study of 767 cases of radical mastectomy showed that in 4.6 per cent metastases to the pleura developed within five years of surgery and in another 4.5 per cent during the following five years. Metastases to the operated side occurred in 65 per cent of cases, to the opposite side in 20 per cent, and bilaterally in 15 per cent. Only cases without pulmonary metastases have been regarded as pleural carcinosis. Of 35 cases of pleural carcinosis only 6 (17.1 per cent) were alive one year after the diagnosis was made. One patient survived five years and her pleural metastases were seen to regress spontaneously.—*Spontaneous regress of pleural carcinosis in breast cancer, B. A. Norhman, Acta radiol., January, 1950, 33: 12.*—*(L. Levin)*

Mediastinal Parathyroid Adenoma.—A routine chest roentgenogram of a 50-year-old white man showed a mass in the left anterior mediastinum. Roentgen irradiation of the tumor was followed by weakness, anorexia, vomiting, and sudden death of the patient. The findings at autopsy were: (*1*) a mediastinal parathyroid adenoma, 7 cm. in diameter, chief cell type, with cystic changes; (*2*) nephrosis with foci of medullary calcification and subacute interstitial nephritis; (*3*) petechiae in the heart; (*4*) congestion of the viscera; and (*5*) healed pulmonary tuberculosis. It is suggested that increased secretion or liberation of parathyroid hormone due to irradiation was the cause of death.—*Mediastinal parathyroid adenoma; report of a case with unusual fatal course, W. Staub, D. M. Grayzel, & P. Rosenblatt, Arch. Int. Med., May, 1950, 85: 765.*—*(G. C. Leiner)*

Bronchiectasis.—Twenty-eight operations for bronchiectasis were performed on 23 pa-

tients. Pneumonectomy was done in one case and either segmental resection or lobectomy in the others. No deaths occurred. All of the patients except 2 with bilateral disease were greatly improved as was shown by decrease in expectoration. Coughing in all patients was lessened but it was the one symptom which persisted longest after removal of the diseased segments. Bilateral operations were done in 4 cases. Postoperative localized and loculated empyema with bronchopleural fistula occurred in 4 patients; one resulted from the removal of a shell fragment at the time of segmental resection. Spontaneous pneumothorax on the seventh postoperative day, with collapse of the remainder of the lung, occurred in one patient. In another case insufficient segments were removed because of inadequate localization preoperatively. This is considered one of the dangers of segmental resection. It is suggested that repeat bronchograms should be done if any doubt exists regarding the extent of the disease.—*Bronchiectasis, H. A. Lyons & T. C. Ryan, U. S. Armed Forces M. J., January, 1950, 1: 30.*—(*T. H. Noehren*)

Peptic Ulcer of the Esophagus.—Peptic ulcer of the esophagus can no longer be considered a rare lesion. Since 1936, 27 cases have been reported; the most common occurrence was in the age group under ten years. There was coexistent gastric or duodenal ulcer in 4 cases while in 18 others there was short esophagus. The outstanding symptom in children is vomiting. Hematemesis, dysphagia, and epigastric pain were also noted. In adults suffering from short esophagus and peptic ulcer, retrosternal pain on swallowing was the chief symptom. Only a few reported regurgitation and more had hematemesis. The roentgenographic diagnosis is based on the characteristic niche in the esophagus. This usually occurs several centimeters above the cardia and may be hard to demonstrate. Ulceration is accompanied by a constriction which in acute cases is due to edema and inflammatory changes rather than to spasm. In long-standing cases there are infiltrative inflammatory and fibrous changes. Esophagoscopy was done in 16 cases and was found to be positive in 11. Among the etiologic factors discussed, the action of acids on the sensitive esophageal mucosa was considered most important. Rational therapy requires elimination of the factor which is responsible for acid in the esophagus.—*Peptic ulcer of the oesophagus, G. Thomsen, Acta radiol., September, 1949, 32: 193.*—(*L. Levin*)

Cervical Hernia.—A 39-year-old man complained of severe cough increasing in intensity during the previous six years. Recently he had been coughing more than usual and had noted pain in his right shoulder accompanied by a bulging over the right clavicle. The swelling occurred and became larger when he coughed, strained, or cleared his throat. On physical examination, there was a definite bulging above each clavicle on straining or coughing. Crepitation was noted over these bulging areas. A diagnosis of bilateral cervical hernia of the lung was confirmed by roentgenograms taken in inspiration and in deep expiration.—*Cervical hernia of the lung, N. V. Wezel, J. A. M. A., March 18, 1950, 142: 804.*—(*H. Abeles*)

Intrathoracic Intestinal Diverticula.—Three cases are reported in which a diverticulum had extended from the upper portion of the small intestine into the thorax. They are the first to be found in the literature. The diverticula were the size of the intestine, perforated the right crus of the diaphragm, continued upward extrapleurally, and reached the apex in all cases. One was balloon-shaped, one varied in contour, and the third crossed over into the left hemithorax. A portion of the blood supply came from thoracic sources. Symptoms were referable to gas and acid content. The patients were from three and one-half to four years of age. All 3 lesions were successfully removed in one or more operations.—*Thoracic diverticula which originate from the intestine, R. E. Gross, E. B. D. Neuhauser, & L. A. Longino, Ann. Surg., March, 1950, 131: 363.*—(*W. H. Oatway, Jr.*)

Traumatic Bronchial Avulsion.—A 13-year-old boy was seen one hour after being run

over by the wheel of a farm tractor. Cyanosis, shock, emphysema of the neck, and a mediastinal shift to the left were present. A right pneumothorax was found by aspiration and an intercostal water seal cannula inserted. Because of several hemoptyses, evidence of a large right bronchopleural fistula, and failure to improve clinically, a right thoracotomy was performed. The right main stem bronchus was found traumatically avulsed proximal to the origin of the right upper lobe bronchus and the proximal stump had retracted into the mediastinum. The hilar arteries and veins were intact. A right pneumonectomy was performed and the patient made an uneventful recovery. Thirty-eight other cases of traumatic bronchial rupture have been found in the literature with recovery in 19. Most cases recovering required eventual surgery for repair of a bronchial stricture or excision of the lung distal to a stricture. No other cases of immediate resection were found.—*A case of traumatic avulsion of a main-stem bronchus from its lung, treated by immediate pneumonectomy, E. R. G. Kirkpatrick, Brit. J. Surg., January, 1950, 37: 362.*—(*M. G. Carter*)

Blast Injury of the Lungs.—Recent wartime experience with blast injuries to the lung has contributed to knowledge of this condition. Explosion produces a radially extending wave of increased pressure which compresses the chest and ruptures alveolar capillaries. Frequent extrapulmonary blast lesions are ruptured ear drums and hemorrhage from abdominal viscera. A case selected from the Texas City disaster of 1947 manifested otorrhea, renal hemorrhage, and pulmonary hemorrhage. The pulmonary hemorrhage progressed for several days, segmental atelectasis developed, and hydropneumothorax appeared. Resolution followed with minimal pleural and pulmonary scarring. This was the only one of 8 cases of so-called blast injury of the lungs due to this disaster which showed no sign of local external or bony trauma to account for the pulmonary lesions (Authors' summary).—*Blast injury of the lungs with report of a case occurring in peace time, M. Schneider & C. P. Klein, Radiology, April, 1950, 54: 548.*—(*W. J. Steininger*)

Pulmonary Decortication in Children.—In 7 children, ranging in age from five months to twelve years, a postpneumonic empyema was converted into a sterile fibrinofibrothorax following an average of thirty days' treatment with sulfonamide compounds and penicillin given systemically. Penicillin was used intrapleurally in only 2 of these children. Surgical pulmonary decortication in these patients produced complete expansion of the lung with obliteration of the pleural space. The average period of postoperative hospitalization was nine days. In 2 children, aged two and six years, there was failure to sterilize the empyema space with a sulfonamide as well as topical and systemic use of penicillin. Decortication resulted in immediate complete expansion of the lung. One child, aged twelve years, developed a chronic empyema and bronchopleural cutaneous fistula. Pulmonary decortication resulted in complete expansion of the lung, closure of the fistula, and obliteration of the pleural space.—*Pulmonary decortication for fibrinofibrothorax and empyema in children, K. P. Klassen, Surgery, February, 1950, 27: 235.*—(*M. G. Carter*)

Valvulotomy for Mitral Stenosis.—Eight patients with mitral stenosis in whom the over-all prognosis without operation was poor underwent valvulotomy of the mitral valve. Several factors were considered in advising operation. The presence of active rheumatism was a definite contraindication. Marked aortic regurgitation was considered a contraindication as was marked mitral regurgitation with secondary dilatation and hypertrophy of the left auricle. Mitral valve calcification was not a definite contraindication. Early pulmonary hypertension was a strong indication for operation. Auricular fibrillation indicated that the optimum time for surgical intervention had passed, since it predisposed to thrombus formation which introduced the additional hazard of embolization. Severe right-sided failure might increase the operative risk prohibitively.

The state of the myocardium was also an important consideration. Among 8 patients operated upon, 2 died, one on the day following operation, the second four days after operation due to a hemorrhage complicating heparin therapy begun because of a cerebral embolus. One other patient suffered a cerebral embolus but made a complete recovery. The 6 survivors followed for periods varying from eight to twenty months all showed marked clinical improvement and were able to resume relatively active lives. Information gained from cardiac catheterization was of extreme importance. The best results were to be expected from those patients in whom the resting pulmonary arterial pressure was low but in whom there was a sharp rise following exercise. If the pulmonary arterial pressure remained elevated following the procedure, the late results of the operation were disappointing. Studies of cardiac output with and without exercise both before and after operation gave valuable information.—*Valvulotomy for mitral stenosis, report of six successful cases, C. Baker, R. C. Brock, & M. Campbell, Brit. M. J., June 3, 1950, No. 4665: 1283.*—(*E. A. Riley*)

Roentgenographic Examination in "Pneumonia".—A total of 228 patients with the clinical diagnosis of pneumonia was referred to a chest clinic for roentgenographic examination. Normal resolution of the pneumonia occurred in 127; 29 patients showed delayed resolution; 7 developed empyema associated with the pneumonia; and 5 developed sterile serous effusions. Pulmonary tuberculosis was found in 32 and was active in 25, in one patient apparently reactivated by the pneumonia. In these patients the illness was sufficiently acute to suggest clinically a pyogenic process. Eleven patients had bronchiectasis and 6 idiopathic pleural effusions presumably on a tuberculous basis. There were 4 patients with new growths, one with a lung abscess, one with a spontaneous pneumothorax, 2 with acute pulmonary edema, one with a pulmonary infarction associated with auricular fibrillation, and one with a cough fracture. The findings justified roentgenographic studies in patients with symptoms suggesting pneumonia, if only as a method of diagnosing tuberculosis.—*X-ray examination in "pneumonia", N. Wynn-Williams, Brit. M. J., March 11, 1950, No. 4653: 579.*—(*E. A. Riley*)

Pulmonary Hodgkin's Disease.—A survey of 35 cases of Hodgkin's disease of the lung demonstrated the striking variability of the roentgen appearance. Some cases were roentgenographically indistinguishable from tuberculosis, pulmonary abscess, peribronchial inflammatory disease, lobar pneumonia, metastatic disease of the lungs, mycotic infection, and miliary sarcoidosis. There were 5 general types of parenchymal involvement: (*1*) direct invasion of the lung in the presence of mediastinal nodal disease; (*2*) peribronchial infiltrates; (*3*) massive homogeneous infiltrates (so-called "lobar infiltrates"); (*4*) lobular infiltrates; and (*5*) general dissemination. The lobular infiltrate was encountered most frequently in this series. Of the 35 cases reviewed, 12 received radiation therapy only. In 3 the response was excellent, in 4 good; and in the remaining 5, the response was slight or undetectable. Ten cases received nitrogen mustard treatment. In 8 cases the improvement was excellent; in the remaining 2 the clinical response was good, but no radiographic evidence of improvement was demonstrable. The development of pulmonary lesions in Hodgkin's disease worsens the prognosis.—*Hodgkin's disease of the lung: Roentgen appearance and therapeutic management, A. Sheinmel, B. Roswit, & L. R. Lawrence, Radiology, February, 1950, 54: 165.*—(*W. J. Steininger*)

Pulmonary Arteriography in Bronchial Carcinoma. Pulmonary arteriography demonstrated diminished vascularity of the involved lung distal to the tumor mass in 14 of 15 cases of bronchial carcinoma. This change was explained by obstruction or compression of arterial branches, bronchial obstruction with resultant emphysema, and necrosis of the pulmonary parenchyma. Other changes encountered less frequently include decreased

caliber of vessels with displacement, distortion, and obstruction of main pulmonary artery. Diminished vascularity was found to occur also in nonneoplastic diseases, notably in senile pulmonary emphysema, bullous emphysema, and lung abscess. However, these conditions were rarely associated with a tumefactive process and no difficulty was encountered in distinguishing the pattern from that produced by carcinoma. Pulmonary arteriography should be added to the diagnostic armamentarium in cases of bronchial carcinoma. The pulmonary vascular pattern shows, in nearly all cases, characteristic deviations from the normal.—*Diagnostic value of pulmonary arteriography in bronchial carcinoma, P. G. Keil, C. A. Voelker, & D. J. Schissel, Am. J. Med. Sc., March, 1950, 219: 301.*—(*W. J. Steininger*)

Subclavian Angiography.—In order to visualize lesions, chiefly tumors, of the parathyroid glands, the posterior and lower parts of the thyroid, and the thymus, angiography by injection of contrast material into the subclavian artery is proposed. In order to prevent arterial spasm, 8 to 10 cc. of a 2.5 per cent solution of papaverin hydrochloride are injected intramuscularly into adult subjects one hour before the catheterization. Under strict aseptic precautions and using local anesthesia, the radial artery is exposed and ligatured in the proximal part of the forearm. A second ligature is placed loosely proximally to the first ligature. A small incision is made in the artery between the ligatures, the proximal being drawn to strangulate the artery temporarily. A ureteral catheter is inserted through the incision and guided under fluoroscopic control into the subclavian artery. Fifteen cc. of 35 per cent solution of Umbradil (Astra) then are injected as rapidly as possible, and two pictures are taken, one at the completion of the injection and another three to four seconds later. After the withdrawal of the catheter the proximal ligature is drawn. No vascular disturbances have been encountered following the ligature of the radial artery. —*Subclavian angiography by arterial catheterization, S. Radner, Acta radiol., December, 1949, 32: 359.*—(*L. Levin*)

Angiocardiography in Coarctation of the Aorta.—The advent of surgical relief for coarctation of the aorta makes its diagnosis of more than academic importance. The exact location of the constriction, the size of the aorta above and beneath the coarctation, the development of the collateral circulation, and the size and position of the innominate, left common carotid, and subclavian arteries should be recognized radiologically. Angiocardiographic observations in 3 patients with coarctation of the aorta demonstrated the size of the coarctation in each, the component parts of the heart and the vascular pedicle were opacified. In addition, the collateral circulation and the descending aorta were visualized.—*Angiocardiography: Its application to the diagnosis of coarctation of the aorta, B. S. Epstein, Radiology, February, 1950, 54: 211.*—(*W. J. Steininger*)

Death Following Angiocardiography.—A survey was attempted of all centers in the United States, Canada, Great Britain, and Sweden using angiocardiography. A total of 6,824 examinations was reported with death in 26 cases, none later than June 30, 1949. Three deaths were in cases complicated by other factors and have been omitted from the discussion. In 21 of the remaining 23 cases, congenital heart disease was present, 17 of these patients were cyanotic and 5 were extremely ill. Seventeen of the deaths occurred in children under eight years of age, all with congenital heart disease, 14 of whom were cyanotic. No deaths were recorded in persons with healthy hearts except one, in a case of renal arterial disease. The commonest form of death reported was sudden respiratory arrest immediately or shortly after injection of the contrast substance. Post-mortem examination was done in all but one case; the cause of death was rarely found. In approximately one-half of the cases there was some clinical or post-mortem evidence to suggest that the respiratory system was susceptible to injury,

and pulmonary edema was reported several times. Subdural hemorrhage occurred twice. The nature of the contrast medium, the number of injections, premedication, or general anesthesia did not influence angiocardiographic mortality. The incidence of death was higher in children, in patients with congenital heart disease, in patients receiving larger doses of contrast subetances, and in those examined in the horizontal posture.—*Death following angiocardiography, C. T. Dotter & F. S. Jackson, Radiology, April, 1950, 54: 527.*—(*W. J. Steininger*)

Rotation Treatment of Esophageal Cancer.—Some of the difficulties encountered in the roentgen therapy of deep-seated cancers have been of a purely physical nature, caused by the distribution and absorption of radiation in the tissues. The modern cross-fire technique has attempted to eradicate these difficulties and to improve the depth effect. The rotation, or convergence, technique of irradiation was first suggested in 1913. Its principle is the movement of the roentgen tube in relation to the patient during the treatment. The advantage of rotation irradiation is that there is ideal distribution of radiation with a maximum depth dose and a low skin dose Conditions for this type of irradiation are favorable insofar as the organs of the thorax are concerned because the air spaces of the lungs counteract the incongruence of the thorax and the distribution of radiation approaches that of the circular, cylindrical phantom. By fluoroscopic means the patient is examined with a contrast medium in the esophagus and the tumor localization is marked on the surface of the thorax in two projections at right angles. Roentgenograms determine the size of the axis field, and the daily dose and irradiation plan are fixed in such a way as to give a tumor dose of approximately 5,000 to 6,000 r in the course of 30 to 40 days. The patient is placed in a rotating chair, the seat of which may be moved in two planes at right angles. The patient is so placed in the chair that the tumor is in the axis of the chair and forms the center of rotation. Of 217 patients treated for cancer of the esophagus and cardia, 137 were men and 80 women. The average age was 66.6 years at the time of admission. The average time elapsed from the first symptom to admission was approximately five months. Ten per cent of the tumors were situated in the upper third of the esophagus, 30 per cent in the middle third, and 36 per cent in the lower third. Twenty-five per cent of the cases were cancers of the cardia, which had the highest incidence in men. Of 111 tumors subjected to microscopic examination, 31 were prickle-cell carcinomas, 31 basal-cell carcinomas, 12 adenocarcinomas, and 38 solid, less differentiated carcinomas. While the palliative effect has been excellent, the curative effect has not been very considerable. The average duration of life has been almost doubled. In more than 20 per cent of all the patients it has been possible to destroy the tumor locally so that no remnants of malignant tissue were demonstrable even by histologic specimens. Only a few patients were cured; the rest died from distant metastases. It is of extreme importance to induce patients with esophageal carcinoma to present themselves for treatment as early as possible, for by shortening the pretreatment period there is hope of obtaining far better results.—*Rotation treatment of cancer of the esophagus, C. Krebs, H. Nielsen, & P. Andersen, Acta radiol., October, 1949, 32: 304.*—(*L. Levin*)

Dicumarol and Roentgen Therapy.—The effect of dicumarol in preventing post-irradiation tissue changes in the human lung is demonstrated in 3 cases of carcinoma of the esophagus and 6 cases of carcinoma of the lung. The dosage of roentgen therapy was massive enough to produce marked destruction of the esophageal tumors. Doses of 5,000 to 8,000 roentgens were used through multiple portals in the treatment of the lung tumors. All cases showed a definite decrease in the size of the tumor. Autopsy was performed in one of the cases of esophageal carcinoma and 3 of pulmonary carcinoma. Microscopic sections showed no evidence of radiation reaction in the alveoli, capillaries, or pleura. One case of

carcinoma of the lung was treated in a similar manner but without the associated dicumarol therapy. During the treatment this patient developed radiation pneumonitis. At autopsy, there was gross and microscopic evidence of pulmonary fibrosis and obliterative fibrous pleuritis attributable to the roentgen therapy. —*Use of anticoagulant (dicumarol) in preventing post-irradiation tissue changes in the human lung, S. H. Macht & H. Perlberg, Jr., Am. J. Roentgenol., March, 1950, 63: 335.*—(*T. H. Noehren*)

ANTIMICROBIAL THERAPY

Intermittent Dosage with Streptomycin.—An attempt was made to avoid or delay the emergence of streptomycin-resistant tubercle bacilli by schemes of intermittent dosage. Forty-five cases of acute progressive bilateral tuberculosis in young persons were alloted at random to one of 4 dosage groups divided as follows: one group received 0.5 gm. of streptomycin six-hourly in alternate weeks, a second group received 0.5 gm. of streptomycin six-hourly in alternate months; a third group received 0.25 gm. of streptomycin six-hourly without intermission; and the fourth group received 1 gm. in a single daily dose without intermission. These regimens were continued for 168 days until all patients had recieved the same total dose. There was no evidence that any of the 4 dosage regimens delayed or avoided the emergence of streptomycin-resistant tubercle bacilli nor was there any difference among the groups in the degree of streptomycin resistance shown by the bacilli. One gram of streptomycin daily in a single injection without intermission of treatment was the most satisfactory dosage scheme for the drug in the therapy of pulmonary tuberculosis. The findings suggested that replacement of a streptomycin-sensitive bacterial population by streptomycin-resistant forms continues to at least some extent during intermissions in treatment.—*Intermittent dosage in the treatment of pulmonary tuberculosis with streptomycin, J. R. Bignall, J. W. Clegg, J. W. Crofton, B. J. Douglas Smith, H. D. Holt, & D. A. Mitchison, Brit. M. J., May 27, 1950, No. 4664: 1224.*—(*E. A. Riley*)

Tuberculous Meningitis in Children.—The early diagnosis of tuberculous meningitis is most likely to be made in children already known to be tuberculous, as the most common early complaints may be general symptoms such as fever, vomiting, somnolence, or irritability. In children not known to be tuberculous, the routine use of a tuberculin skin test in cases of persistent fever or unexplained illness should result in a greater number of early diagnoses of tuberculous meningitis. Chest roentgenograms show evidence of tuberculosis in more than 90 per cent of cases of tuberculous meningitis; manifest primary tuberculosis is present in more than 75 per cent. Children with primary tuberculosis should have spinal fluid examinations whenever the suspicion of meningitis is aroused by general symptoms. Serous tuberculous meningitis should not be mistakenly treated as tuberculous meningitis since the prognosis is not as grave. Spinal fluid pressure and the number of cells increase in either form of meningitis but there are no changes in chemical constituents in serous meningitis, the sugar, protein, and chloride content remaining within normal range. Early diagnosis with prompt and adequate therapy are important. The use of intrathecal therapy in addition to intramuscular treatment seems clearly indicated. Of 18 children with tuberculous meningitis treated with streptomycin and continued on Promizole given orally, 13 survived nine to twenty-seven months after the initial diagnosis. All are mentally normal, 4 have neurologic residuals, none seriously crippling. All children, regardless of age or size received streptomycin, 1 gm. daily, for 180 days. The intrathecal dosage was 0.1 gm. daily for 40 days. In addition, Promizole was given orally every six hours. An initial daily dose of 0.5 to 1.0 gm. daily was administered; in the absence of toxicity this was gradually increased until a blood level of 1.0 to 3.0 mg. per 100 cc. was obtained. Few toxic effects have been noted. The addition of adequate amounts of Prom-

izole to streptomycin would seem to be of advantage in the treatment of tuberculous meningitis.—*The diagnosis and treatment of tuberculous meningitis in children, E. M. Lincoln & T. W. Kirmse, Am. J. Med. Sc., April, 1950, 219: 382.*—(*W. J. Steininger*)

Miliary and Meningeal Tuberculosis.—In a two-year follow-up study of 100 patients with miliary and meningeal tuberculosis treated with streptomycin in Veterans Administration hospitals, 21 are living 19 to 28 months after the end of treatment. The daily intramuscular dose of streptomycin was 1.8 gm. administered from 100 to 185 days; in cases of meningitis, the intrathecal dose was 50 to 100 mg. injected 3 to 7 times weekly for a total of 45 to 102 injections. There is a marked difference in survival rates among the 3 major forms of fatal tuberculosis included in the series. Acute disseminated miliary tuberculosis was "cured" in somewhat more than 50 per cent of the cases. In instances in which meningitis existed alone, approximately 20 per cent survived. Less than 10 per cent of cases with combined miliary and meningeal tuberculosis survived. Approximately two-thirds of the patients with miliary tuberculosis developed meningitis and when it occurred the chance of recovery was markedly diminished. Since it is desirable to treat meningitis as soon as possible after its development, diagnostic lumbar punctures should be performed at routine intervals in individuals being treated for miliary tuberculosis. In the present series, only those patients of the 81 with meningitis survived who received at least 45 separate intraspinal injections of streptomycin. A significant advancement in the management of miliary and meningeal tuberculosis has been accomplished. With further manipulation of streptomycin dosage schedules, further gains may be expected. A more likely approach seems to lie in the intelligent use of adjunctive materials: fibrinolysins (streptokinase), anticoagulants, accessory antibacterial agents (sulfones, para-aminosalicylic acid), and possibly other mechanical or surgical measures. It is hoped, of course, that a better and more tuberculocidal material is forthcoming.—*Two-year follow-up report of patients with miliary and meningeal tuberculosis treated with streptomycin, P. A. Bunn, Am. J. Med. Sc., February, 1950, 219: 127.*—(*W. J. Steininger*)

Streptomycin for Miliary Tuberculosis.—A total of 25 cases was treated. The criteria for selection of the cases were (*1*) typical roentgenographic appearance, (*2*) additional or presumptive evidence of tuberculosis, and (*3*) the acute nature of the condition. Cases with meningitis on initial examination were not included. Bacteriologic proof of tuberculosis was forthcoming on admission in 14 cases and in 7 others eventually. The Mantoux test was positive in 18 of the 19 cases tested. The treatment consisted of streptomycin, 2 gm. daily, for adults and correspondingly smaller doses for children. It was continued for at least three months. All cases, including the fatal ones, showed good clinical and radiographic response to treatment. There were 14 survivors, including 9 with uninterrupted recovery, 4 who developed meningitis, and one who developed pulmonary tuberculosis. There were 11 deaths including 3 who died within the first week and 4 who developed meningitis. The prognosis was worst in children below the age of two years and in those who were most acutely ill on admission.—*Streptomycin in acute miliary tuberculosis: Report to Medical Research Council, Lancet, May 6, 1950, 1: 84.*—(*A. G. Cohen*)

Streptomycin for Tuberculous Cavities.—Of 110 tuberculous cavities treated with streptomycin, 14 per cent showed closure confirmed by tomography. Two of the cavities reappeared two and four months later. In the 14 others the cavities remained closed after an observation period of six months. Marked diminution in size occurred in 23 per cent of the cavities; in the remaining 62 per cent, streptomycin was without effect. The majority of cavities responding to streptomycin were of recent origin. Cavities closed with streptomycin in 23.4 per cent of cases when not older than three months. Older cavities closed

only in 7 per cent of cases. Total doses of more than 60 gm. of streptomycin were necessary in order to obtain these results.—*L'action de la streptomycine sur les tuberculoses cavitaires, Pierre-Bourgeois, G. Canetti, R. Genevrier, & R. Colle, Rev. de la tuberc., 1950, 14: 15.*—(*V. Leites*)

Streptomycin for Tuberculous Cavities.—Ninety cases of tuberculous cavitary lesions were treated with streptomycin. In 50 of these, the cavities were of recent origin (less than six months). Cavity closure was always determined by tomography and gastric culture. The observation period ranged from six to sixteen months. Cavity closure occurred in 10 of the 90 cases, 7 of the 10 cavities being of recent origin. In 11 cases there was diminution in the size of the cavity, in 57 it remained unchanged. In 12 cases the cavity diameter increased. When re-examined after eighteen to thirty months, only 7.8 per cent of all patients had maintained cavity closure. The duration of treatment varied from three to four months with a total dose of 120 to 190 gm. of streptomycin.—*Sur la streptomycinothérapie des cavernes tuberculeuses. Résultats immédiats et tardifs, E. Bernard, B. Kreis, A. Lotte, P. Y. Paley, & G. Fosse, Rev. de la tuberc., 1950, 14: 3.*—(*V. Leites*)

Streptomycin for Tuberculous Cavities.—The usefulness of streptomycin in cavitary is determined by 2 facts: (*1*) the extremely limited effect of streptomycin on tuberculous cavities, at least with the present dosage, the results are not superior to those obtained with simple bed rest; (*2*) the emergence of resistance which occurs with particular rapidity in cavities. In the presence of an isolated cavity without great constitutional disturbances, there is no indication for the use of streptomycin. If the cavity is associated with pulmonary lesions of pneumonic or nodular character, a pneumothorax is first attempted and if a good collapse is obtained streptomycin is started. If the pneumothorax is unsatisfactory streptomycin is reserved for the time of surgery. It is inadvisable to proceed in the inverse order, i.e., to start streptomycin with the view of clearing up infiltrations and of "cooling off" the acute exacerbation before starting pneumothorax.—*Le traitement des cavernes en fonction de la notion de la streptomycine-resistance, A. Meyer, M. Brunel, & J. Chretien, Rev. de la tuberc., 1950, 14: 104.*—(*V. Leites*)

Intracavitary Streptomycin.—A new method for treating giant cavities was introduced by Zorini and Botari of the Forlanini Institute in 1947. This was a combination of cavitary lavage and aspiration with intracavitary administration of streptomycin followed by a thoracoplasty with apicolysis. Streptomycin, 0.5 gm., in a 25 per cent solution was introduced through a trocar directly into the cavity. Simultaneously streptomycin, 1 gm., was given parenterally. Of 66 cases so treated, only 4 showed cavity closure after intracavitary streptomycin alone, without surgery. The antimicrobial treatment was carried out several weeks prior to thoracoplasty and continued after the operation until acid-fast bacilli persistently disappeared from the expectoration and the endocavitary secretions.—*Streptomycine endocavitaire, A. O. Zorini, Rev. de la tuberc., 1950, 14: 251.*—(*V. Leites*)

Streptomycin for Anorectal Tuberculosis.—Among patients with pulmonary tuberculosis, there were 23 cases of various tuberculous lesions around the rectum and anus. These were treated either with streptomycin alone, streptomycin and surgery, or surgery alone. Of 15 cases of perianal sinus with or without abscess treated with streptomycin, 5 healed without surgery and 9 with simple incision and drainage. Heretofore, radical surgery usually was required. Two fistulas healed without surgery which was unusual previously. Superficial anal ulcers and fissures as well as ulcers in the mucosa of the rectum and sigmoid healed promptly and completely after streptomycin therapy. Subjectively, the patients suffered from much less pain both before and after surgery. In a few cases, an abscess formed during streptomycin therapy for pulmonary tuberculosis.—*Streptomycin in the treatment of*

tuberculosis of the rectosigmoid region and anus, C. L. Martin, Surg. Gynec. & Obst., June, 1950, 90: 681.—(A. G. Cohen)

Screening for Antituberculous Drugs.—A rapid method for observing the effect of antituberculosis agents is offered, utilizing standardized experimental tuberculous infections in the cornea of mice. Drugs so tested were streptomycin, sodium *p*-aminosalicylate, sulphetrone, and combined sodium *p*-aminosalicylate with streptomycin. Streptomycin prolonged the incubation period of the infection, and reduced the size of the lesions when they appeared; some animals did not develop lesions at all. Sodium *p*-aminosalicylate gave similar but less marked inhibitory results. Sulphetrone did not inhibit the appearance of lesions in more than half the animals, but the subsequent lesions were smaller than in the controls. Combined streptomycin and sodium *p*-aminosalicylate gave an enhanced inhibitory effect, but the relapse rate after treatment was the same as with streptomycin alone.—*Experimental infections of the cornea of the mouse: A screening test for antituberculous substances, R. J. W. Rees & J. M. Robson, Brit. J. Pharmacol., 1950, 5: 77.—(A. A. Cohen)*

Streptomycin in Experimental Tuberculosis.—Mice were infected with one of 3 bacterial strains: virulent human bacilli (H 512), BCG, and paratubercle bacilli. The minimal therapeutic dose of streptomycin was determined for these infections. (*1*) For human strain H 512 the minimal daily therapeutic dose of streptomycin was approximately 500 units. With this dosage there were 50 per cent survivals. The mortality was 100 per cent with 100 units. No deaths occurred with doses of 1,000 to 2,000 units for 45 days. (*2*) For BCG, the intensity of microscopically demonstrable lesions varied in the untreated controls between 1+ and 3+ in 77 per cent of the mice. The same incidence was found in animals receiving 100 units of streptomycin daily whereas of the animals treated with 500, 1,000 or 2,000 units, only 27 to 37 per cent showed lesions of this intensity. In regard to the bacillary content of the lungs it also appeared that doses from 500 to 2,000 units had a definite antibacterial effect, whereas doses below 500 units were almost ineffective. (*3*) For paratubercle bacilli no animals died when treated with 500 to 1,000 units daily. In the other groups 21 to 26 per cent died. The incidence of neurologic manifestations (tremor, lack of coordination, deviation of the head, rolling around the anteroposterior axis) increased with decreasing doses of streptomycin. The incidence of renal lesions was 7.1 per cent in animals treated with 2,000 units daily, 26.7 per cent with 1,000 units, 79 per cent with 100 units, and 88 per cent for untreated controls.—*Effets antituberculeux exercés par la streptomycine chez les souris contaminées par les souches de bacilles acide resistants H 512, BCG, et 607, C. Levaditi & A. Vaisman, Ann. Inst. Pasteur, March, 1950, 78: 407.—(V. Leites)*

Neomycin Experimentally.—The administration of neomycin has been found to increase the survival time of mice infected either intravenously or intracerebrally with virulent human-type tubercle bacilli. This work shows that its administration to tuberculous guinea pigs had a marked beneficial effect on the disease even when treatment was delayed until the infection was well established. Little grossly evident disease was found in the animals treated with streptomycin or neomycin. Microscopically it was found that neomycin was capable of reversing the progressive disease, though its effect was possibly not as great as that of streptomycin. It appears that neomycin is effective against streptomycin-resistant tubercle bacilli.—*Neomycin in experimental tuberculosis in guinea pigs, A. G. Karlson, J. H. Gainer, & W. H. Feldman, Dis. of Chest, May, 1950, 17: 493.—(E. A. Rouff)*

Therapy of Lung Abscess.—The current trend is toward medical treatment of lung abscess. The results in the cases treated earlier indicate that the dosage of penicillin used was insufficient. Patients now receive two million

units daily, divided into four doses at intervals of six hours, for at least three weeks and usually for not more than four weeks. Also, postural drainage is given many hours a day. The cases must be followed for at least a year. Thirty-two cases were treated, 7 surgically and 25 with penicillin and postural drainage. Six cases were treated with less than one million units daily, 3 were cured and 3 developed bronchiectasis. Of the 19 cases treated with higher doses, 15 were cured, 2 became chronic, one developed bronchiectasis, and one died. Seven patients received surgical drainage; 3 were cured and 4 developed bronchiectasis. Patients treated medically became ambulant much sooner. Residual changes following any method of treatment are an indication for resectional surgery.—*Therapy of lung abscess, A. N. Sutherland & L. J. Grant, Lancet, March 25, 1950, 1: 530.*—(*A. G. Cohen*)

LABORATORY STUDIES

Cortisone in Tuberculin Hypersensitivity.—In rabbits and guinea pigs sensitized with tubercle bacilli (BCG), dermal reactivity to Old Tuberculin (OT) and to cytoplasmic particles from tubercle bacilli as well as systemic shock produced by intraperitoneal injection of OT could be suppressed by treatment with cortisone. Four days after cessation of treatment the skin test again became positive. Cortisone did not prevent anaphylactic shock in guinea pigs sensitized with normal horse serum nor did it exert any influence on either the appearance of the Arthus reaction in rabbits injected with normal horse serum or on the skin test reaction to an intradermal injection of normal horse serum in these rabbits.—*Effect of cortisone on some reactions of hypersensitivity in laboratory animals, S. Harris & T. N. Harris, Proc. Soc. Exper. Biol. & Med., May, 1950, 74: 186.*—(*F. B. Seibert*)

Stability of Tuberculin.—Tuberculin can still be found in stable form in the liquid nutrient medium kept more than eight years at incubator temperature. In buffered solutions of pH 7.0, free from preservatives or contaminants, and in sealed amber glass ampules to avoid evaporation, tuberculin solutions are stable biologically for more than nine years at room and refrigerator temperatures but not at incubator temperatures. Dilutions in unbuffered saline solution are not stable. Heating of tuberculin in the natural filtrate from a 2-month-old culture of human tubercle bacilli at or below pH of 6.0 results in a loss of tuberculin from the solution. The effect of heat is less appreciable upon an 8-year-old culture, maintained at 37°C., in that a lower pH is required to cause precipitation and tuberculin loss. It is concluded that tubercle bacilli possess autolytic enzymes capable of producing tuberculin *in vitro* but not capable of degrading further the specific, biologically active protein.—*The stability of tuberculin, H. J. Corper & M. L. Cohn, Tubercle, June, 1950, 31: 122.*—(*A. G. Cohen*)

Hemagglutinins in Tuberculosis.—Utilizing a very concentrated Old Tuberculin (Lederle) as an antigen in the hemagglutinin test of Middlebrook and Dubos, the sera of 216 normal adults and patients with syphilis or nontuberculous chest diseases were tested and 203 showed no reactions; 12 had positive reactions in serum dilution of 1:2; and one in dilution of 1:4. Of sera from 168 patients with active tuberculosis, 92 per cent gave positive reactions in dilutions ranging from 1:8 to 1:512. Sera from 33 apparently cured tuberculous individuals revealed no reactions in 31 and positive reactions in 2 in a serum dilution of 1:2. This hemagglutination reaction is apparently a relatively specific test for active tuberculosis.—*Practical application of a hemagglutination reaction in tuberculosis, S. Rothbard, A. S. Doomeief, & K. E. Hile, Proc. Soc. Exper. Biol. & Med., May, 1950, 74: 72.*—(*F. B. Seibert*)

Hemagglutinin Reaction.—Hemagglutinin reactions can be obtained with precipitated tuberculin 1:100 from the Pasteur Institute. The original technique described by Middlebrook and Dubos can be utilized by sensitizing 0.1 cc. of washed sheep erythrocytes with 0.5

cc. of tuberculin. The results are analogous to those obtained with the antigen extracts prepared by the original method. The results can be read easily; the titer of hemagglutination after 24 hours is comparable with the two antigens.—*Réactions d'hemagglutination pratiquées comparativement avec l'antigène type Middlebrook et Dubos et avec la tuberculine precipitée, C. Gernez-Rieux & A. Taquet, Ann. Inst. Pasteur, April, 1950, 78: 550.*—(*V. Leites*)

Hemagglutinin Reaction.— The sensitization of sheep red blood cells with antigen from tubercle bacilli is a complicated procedure. The authors have modified the technique of Dubos and Middlebrook by employing purified tuberculin from the Pasteur Institute as the "sensitizing" agent. In 17 cases of active pulmonary tuberculosis, 8 positive and 9 negative reactions were observed. Eight of the 9 negative reactions occurred in cases of very severe ulcerocaseous disease mostly in the terminal stage. Three cases of serofibrinous pleurisy gave positive reactions. No positive reactions were found in 10 nontuberculous cases. In 130 healthy adults there were 121 negative reactors; 74 of these had a positive tuberculin test. Of 19 healthy persons with a positive hemagglutinin test, 12 had a positive tuberculin test and 16 had a positive BCG tuberculin test.—*Réaction d'hémagglutination type Dubos-Middlebrook realisée avec une tuberculine purifiée, résultats obtenus, R. Sohier, J. Juillard, & J. Trimberger, Ann. Inst. Pasteur, February, 1950, 78: 283.*—(*V. Leites*)

Studies with Viscous Umbradil.—Umbradil is a new roentgenographic contrast medium which is viscous, water-soluble, and easily resorbed. It consists of Umbradil (diethanolamine salt of 3,5-di-iodo-4 pyridine-N-acitic acid), mixed with a viscosity-increasing substance, carboxymethylcellulose. In spite of the rather high viscosity, the surface tension of the material is relatively low so that it can reach even the smaller pockets and very narrow channels such as the finer branches of the prostatic gland ducts. Umbradil proper is excreted by the kidneys while the carboxymethylcellulose is taken up by phagocytes within the pulmonary alveoli. The material is especially well suited for examination of the bronchial tree, male and female sex organs, ducts of different glands, and fistular tracts. It is not suitable for myelographic studies. The only absolute contraindication to its use in making bronchograms is the presence of upper respiratory infections, as pneumonia may follow. It is used to cover the mucosa with a thin layer of opaque material without clogging the bronchial tubes.—*Further studies with viscous Umbradil (Umbradil-Viskös), O. Morales, Acta radiol., October, 1949, 32: 318.*—(*L. Levin*)

Studies with Viscous Umbradil.—Umbradil-Viskös B, a new radiopaque contrast medium, and its components were investigated by injection into the lungs of white rats and rabbits to ascertain the reaction of the lung to these materials. Histologically the changes seemed to be nonspecific and could also be produced on injection with physiologic saline solution. There was thickening of the alveolar system and increased blood content, but these disappeared promptly. The changes were, however, of such a nature that they might cause temporary lowering of function in the affected area.—*The reaction of the lung on bronchography with viscous Umbradil (Umbradil-Viskös B) (Astra), Umbradil (Astra), and carboxymethylcellulose, B. Hellstrom & H. Holgren, Acta radiol., December, 1949, 32: 471.*—(*L. Levin*)

Polythene Prosthesis after Pneumonectomy.—An experimental study with rats has demonstrated the usefulness of a lung-sized Polythene prosthesis placed in the pleural cavity after pneumonectomy. There is a benign pleural reaction to such a prosthesis. The amount of exudate is not significantly increased over that seen after ordinary pneumonectomy, and the cell count of the exudate is not significantly altered. A neomembrane forms about the Polythene bag as early as twenty-four hours after operation. This mem-

brane gradually increases in thickness, reaching its maximum about one month postoperatively. In succeeding months it contracts down to a thin fibrinous, rather acellular plaque completely surrounding the bag. This prosthesis effectively prevents extensive shift of the mediastinum and marked overdistention of the remaining lung. After ordinary pneumonectomy, the remaining lung rapidly increases in size and weight, so that by one month postoperatively it weighs almost as much as the combined weight of both lungs in normal rats. This increase in weight of the remaining lung is largely prevented by the use of the Polythene bag.—*Pleural reactions to Polythene prosthesis after pneumonectomy: An experimental study, J. R. Lydell & G. M Higgins, Surgery, March, 1950, 27: 386.—(M. G. Carter)*

Siderosis.—A quantity of dust from the cleaning room of a foundry was found to consist mostly of iron oxide. There was 4 per cent of crystalline free silica. Normal guinea pigs, rats, and rabbits and tuberculous guinea pigs were exposed to the dusts in inhalation experiments lasting up to three years. Several roentgenograms of the rabbits showed fine nodular densities appearing two to three years after the first exposure. Gross and microscopic examination of the lungs showed round or elongated foci of accumulated dust without fibrosis. The radiopacity was due to the fact that iron oxide was a major component of the dust. Similar foci without fibrosis appeared in rats exposed up to eighteen months and in guinea pigs up to three years. The course in guinea pigs was unaltered. It is concluded that iron oxide dust is inert.—*Siderosis: A benign pneumonoconiosis due to the inhalation of iron dust, Part II, A. J. Vorwald, P. C. Pratt, T. M. Durkan, A. B. Delahant, & D. A. Bailey, Indust. Med. & Surg., April, 1950, 19: 170.—(A. G. Cohen)*

Respiration in Exercise.—The multiple factor theory has been applied to an analysis of the regulation of breathing in exercise. It was demonstrated that it is necessary to postulate the existence of an exercise stimulus of potency equal to the metabolic rate ratio and distinct from the arterial chemical agents, pCO_2, H- and pO_2, in order to account for the ventilatory response. It was further shown that the stimulus probably acts in an additive rather than in a multiplicative fashion. This stimulus, together with a lactic acid acidosis, appears to be adequate to account for the hyperpnea of both moderate and severe exercise. Further analysis revealed that information so far available in the literature permits no conclusion regarding either the nature of the exercise stimulus or the pathway through which it operates. The inability of these studies to provide satisfactory answers is primarily because of their failure to consider all of the many factors concerned in the regulation of breathing. The multiple factor theory, by providing a method of analysis in which the influence of 3 of these factors can be quantitatively accounted for, permits a more accurate evaluation of the role of additional factors. The usefulness of this method of approach in studies designed to identify the nature of the exercise stimulus and/or the pathway through which it operates has been demonstrated. It is hoped that this analysis will be of some value not only in the reinterpretation of previous investigations, but also in the design and interpretation of the many future experiments which are urgently needed to provide a satisfactory solution to the problem of exercise hyperpnea (Author's summary).—*Analysis of factors concerned in regulation of breathing in exercise, F. S. Grodius, Physiol. Rev., April, 1950, 30: 220.—(G. C. Leiner)*

Vital Capacity and Position.—Studies of the vital capacity and of the expiratory reserve (the amount of air that can be expelled by a maximal forced expiration following normal expiration) were made in 10 healthy subjects in the erect and in the supine position. In the supine position, there was a mean decrease of 341 cc. in the vital capacity; 184 cc. (54 per cent) of this loss was regained when the supine position was maintained for ten minutes. When the erect position was resumed,

the vital capacity increased over its original erect value, the mean excess being 132 cc. With recumbency, there was a mean decrease of 860 cc. in the expiratory reserve which remained unchanged while the supine position was maintained. When the erect position was resumed, the expiratory reserve remained 171 cc. below its original erect value. A close correlation between the vertical component through which the body moved in assuming the supine position and the diminution of the vital capacity was demonstrated in 6 subjects.—*Change of vital capacity with the assumption of the supine position, W. J. Osher, Am. J. Physiol., May, 1950, 161: 353.*—(*G. C. Leiner*)

Vital Capacity in Heart Disease.—The vital capacity was measured for 389 cardiac patients ranging in age from 20 to 42 years. Of the 321 patients with rheumatic heart disease, 300 had a vital capacity within the normal range and 299 had normal tolerance to exercise. Twenty-one patients had a diminished vital capacity ranging from minus 14 to minus 33 per cent and 18 had a diminished exercise tolerance. The majority of patients with diminished vital capacity had marked cardiac damage and one-third had auricular fibrillation. Only one of the 59 patients with congenital heart disease of the cyanotic type had a diminished vital capacity and a lowered exercise tolerance. There was a close correlation between vital capacity and exercise tolerance in adults with heart disease.—*Vital capacity in adults with heart disease: Its relation to age, degree of cardiac enlargement and type of valvular lesion, J. D. Gardam, Am. J. Med. Sc., January, 1950, 219: 76.*—(*W. J. Steininger*)

Lung Vessel Pressures and Edema.—On the basis of experiments on dogs the following conclusions are made: "The pulmonary edema observed consequent to prolonged inspiratory or expiratory airway resistance is associated with significant elevation in pulmonary venous pressure. Elevation in pulmonary capillary pressure produced is sufficiently great to make the effective filtration pressure larger than the colloid osmotic pressure of dog blood. There is no need to postulate alterations in pulmonary capillary permeability to account for the lung edema observed in the experiments reported."—*Pulmonary vascular pressures in relation to edema production by airway resistance and plethora in dogs, F. J. Haddy, G. S. Campbell, & M. B. Visscher, Am. J. Physiol., May, 1950, 161: 336.*—(*G. C. Leiner*)

Respiration of the Newborn.—The rhythm of respiration of newborn infants during sleep is often irregular. The irregularity may be abolished by giving oxygen and may be produced by lowering the oxygen content of air. The minute volume was decreased about 10 per cent when 12 per cent oxygen was given to a series of 10 infants, 7 of which showed the change. The minute volume was increased about 30 per cent when high concentrations of oxygen (42 to 74 per cent) were used; 8 of the 10 infants showed the change. Five per cent carbon dioxide in oxygen was a uniform stimulant, but also caused crying.—*Respiration of the newborn infant: Variation in respiratory minute volume with change in per cent of oxygen in respired mixture, P. J. Howard & A. R. Bauer, Am. J. Dis. Child., April, 1950, 79: 611.*—(*W. H. Oatway, Jr.*)

Gas Mixing during Respiration.—Rapidly recorded measurements of the nitrogen content and of the expired and inspired volumes were used to study the patterns of gas concentration and volume during single expirations in normal human subjects. To emphasize the patterns due to mixing processes, the subject first cleared his lungs of nitrogen by breathing oxygen; results were recorded when he started breathing air. During ten seconds, only approximately 5 ml. of nitrogen were removed from the lungs by the blood. In a maximal expiration, the records showed three main phases: (*1*) a sloping water-vapor plateau of between 70 and 125 ml., curving downward into (*2*) a rapidly falling nitrogen phase of 100 to 150 ml., which slowly curved into (*3*) a sloping final plateau, starting at 1,000 ml. and continuing to the end of the expiration. By determining the volume of nitrogen inspired

and expired from these records, it was possible to calculate the residual volume and hence the total lung volume at each instant. The slope of the final plateau (per cent nitrogen per liter expired) was taken as a measure of mixing efficiency; a normal, resting expiration did not reach the constant slope seen in a maximal expiration.—*Mixing of gases within respiratory system with a new type nitrogen meter, J. C. Lilly, Am. J. Physiol., May, 1950, 161: 542.—(G. C. Leiner)*

Regulation of Respiration.—Apneusis in the cat is not permanent nor does it supplant completely periodic respirations of a normal type. It diminishes and disappears with return of periodic respirations as deterioration progresses. Apneusis or inspiratory spasm fails to appear in the vagotomized animal when transections are made below the striae acusticae. Apneusis is considered to be an epiphenomenon arising from supramedullary centers and not intrinsically associated with the genesis of respiration. The periodic respiration of the vagotomized medullary preparation has fundamental similarities to normal respiration. Respiration is envisaged as a basic periodicity of the medullary centers regulated secondarily by facilitatory and suppressor areas of the brain stem (Authors' summary). —*Pontine and medullary regulation of respiration in the cat, C. G. Breckenridge & H. E. Hoff, Am. J. Physiol., February 1, 1950, 160: 385.—(G. C. Leiner)*

Changes after Pulmonary Artery Ligation.—A great and rapid rise in the amount of blood circulating through the bronchial arteries results when the pulmonary artery is ligated in the dog. The anatomical changes in the lungs of such animals were studied by preparing durable vinylite casts of the bronchovascular structures. Expansion of the bronchial collateral circulation is well advanced within twelve weeks after ligation of the pulmonary artery; the pulmonary artery does not become thrombosed distally. By 42 weeks, in some animals, precapillary anastomoses with a diameter greater than 50μ develop between the bronchial and pulmonary circulations. These are associated with bronchioles beyond those of the sixth order in relation to the lobar bronchus. The bronchial arteries associated with the terminal bronchi have a larger total cross-sectional area than the pulmonary artery at the same level. This, together with the absence of microscopic changes in the alveoli, suggests that the peripheral resistance to blood flow in the lungs remains low. The extent of the collateral circulation demonstrated anatomically appears to be compatible with the great magnitude of the flow as determined in physiologic experiments. The collateral flow observed in these experiments and thought to occur in congenital pulmonic stenosis and bronchiectasis in man has significant clinical implications in respect to the work of the heart in such conditions.—*Studies on the lung after ligation of the pulmonary artery: II. Anatomical changes, A. A. Liebow, M. R. Hales, W. E. Bloomer, W. Harrison, & G. F. Lindskog, Am. J. Path., March, 1950, 26: 177.—(J. S. Woolley)*

PUBLIC HEALTH AND EPIDEMIOLOGY

Removal of Children for Tuberculous Homes.—This is a follow-up study conducted by the French National Institute of Hygiene on children who were removed from their homes and were placed by the Oevre Grancher in rural homes before 1914. All of the children came from homes where one or both parents had tuberculosis in communicable form. In the majority of cases, tuberculosis was subsequently found to be the cause of death of the sick parent. It was possible to trace 942 persons who had been placed in rural homes and 1,153 who had not been so placed. The maori ty of the placed children were between the ages of five and nine; only 5 per cent were placed under the age of three. The upper age limit for placement was fourteen. In 10.5 per cent of the cases, the source case was already present in the home at birth of the child. In 20 per cent there was exposure before the age of three. Of 675 placed children in whom this information could be obtained, 646 (96 per cent) had been in contact with the source case:

in 37 per cent for less than one year, in 29 per cent for one to two years, in 30 per cent for three years and more. In 47 per cent of instances the child shared the room with the sick parent; in 9 per cent, the same bed. In one-third of the cases the children remained placed for five to ten years; in the remaining two-thirds, the stay was less than five years; in 13 per cent, it was less than one year. Of the 942 placed children, information could be obtained for 898 as to the state of their health during the stay in the foster home. In 895 of these, no serious illnesses were reported during this period. The control group consists of 1,153 children who for various reasons were not placed although they belonged to the same families with one or two tuberculous parents. Of this group, 67 per cent were above or below the age limit for placement at the onset of tuberculosis of the parent. In 38 per cent of these children, the exposure was interrupted by hospitalization of the source case or removal to relatives. The over-all tuberculosis morbidity in this group was 16 per cent; the tuberculosis mortality, 13.5 per cent. In order to eliminate the source of error inherent in the higher tuberculosis mortality of the first two years of life not represented in the placed group, only placed and non-placed individuals from two to twelve years were compared, so that 748 placed children and their 318 non-placed siblings were studied. Of the placed persons, 14.5 per cent had developed tuberculosis as compared to 22 per cent of the non-placed. The tuberculosis mortality in the placed group was 6 per cent and 13 per cent in the non-placed. It is emphasized that these results are only tentative and that all investigations were particularly difficult since two wars have occurred since the placement of the first children.—*Résultats de la prophylaxie anti-tuberculeuse chéz l'enfant par le placement a l'Oevre Grancher, A. Lotte, Semaine d. hôp. Paris, January 2, 1950, 26: 22.*—(*V. Leites*)

Reinfection of Children.—A series of 6,222 children from broken families was examined at the Henry Ford Hospital in Detroit during the past 20 years, before they were placed in foster homes. Tuberculin skin tests and chest roentgenograms were routinely done. The cause for dependency was often the hospitalization of a parent for tuberculosis. A previous report was made in 1940, after twelve years and 4,808 examinations. The current report includes 1,414 children examined between 1940 and 1947. During the first twelve years 17.2 per cent (828) of the children reacted to 0.01 mg. of OT, while only 7.3 per cent (104) reacted during the last eight years. This is thought to be significant and perhaps due to the more regular and rapid segregation of the parents in recent years. Ten reinfection-type lesions were seen in the films at the first examination. In the follow-up studies, 29 reinfection lesions were noted among the tuberculin reactors; 8 of these had no evidence of a primary lesion, while 21 showed evidence of a first infection. None of the tuberculin reactors which were found in the past eight years has yet acquired a reinfection; the 6 new reinfections all came from the 1938–1939 group. A series of 281 children from tuberculous homes had negative tuberculin skin tests; no reinfection lesions appeared in the follow-up films. Further evidence has also been found to bolster the previous conclusion that reinfection tuberculosis develops in adolescents because of nutritional defects. Twenty-one of the 29 lesions occurred in girls, and 12 of these developed in the period of five years which included puberty. The criteria of malnutrition were the nitrogen and calcium balances.—*Tuberculous endogenous reinfection: Twenty year follow-up studies of reactors after removal from contact, J. A. Johnson, P. J. Howard, & B. H. Douglas, Am. J. Dis. Child., March, 1950, 79: 428.*—(*W. H. Oatway, Jr.*)

Relation of Age to Tuberculosis.—Data were assembled from the statistical records of 3,000 children up to 15 years of age and 9,000 adults through 60 years of age to clarify the incidence rate of tuberculous infection at different ages, the development of clinical tuberculosis, and the mortality spread by age and sex. It was found that infection with tuber-

culosis was relatively rare in children, only 1.3 per cent up to 14 years of age being found to have positive skin reactions. After this age the incidence of reaction rose rapidly to its peak around the age of 50 years, there being 74.0 per cent positive reactors up to 59 years. After this the reaction declined to 66.0 per cent beyond the sixtieth year. Males gave slightly more positive reactions up to 30 years and beyond this age were much more often infected. The incidence of clinical disease was also found to be higher in men beyond 30 years of age as was the mortality rate. Before 14 years of age the female was more often infected and the mortality rate was much higher than in later years.—*An analysis of tuberculous infection from birth to old age; its relationship to clinical tuberculosis and deaths from tuberculosis, P. W. Beaven, Dis. of Chest, March, 1950, 17: 280.*—(*E. A. Rouff*)

Histoplasmin and Tuberculin Sensitivity in Brazil.—Of 870 male prisoners in Porto Alegre, Brazil, 127 (14.6 per cent) showed a positive skin reaction to histoplasmin in a 1 per cent dilution. Previous Brazilian workers had found rates varying from 9.24 per cent in Bahia (Pedrosa Cunha) to 26 per cent in the Federal District (Carvallo). In the present group positivity reached its highest in the 36 to 40 age group, a gradual decrease being apparent from then on. Tests with tuberculin up to a 1:10 dilution proved positive in 91 per cent of the histoplasmin-positive group. Racial factors did not affect the results significantly. All histoplasmin-positive patients with residual pulmonary lesions were found to be tuberculin-positive at 1:10 dilution (10 mg.) even when negative at 1:100 dilution. This emphasizes the need of an exhaustive search for residual allergy, with killed BCG if necessary, in apparently tuberculin-negative cases with pulmonary lesions before attributing these to fungus infection. Cross tests with other products in the histoplasmin reactors revealed 12.8 per cent positive to candidin (oidiomycin), 2.6 per cent to paracoccidioidin, 1.7 per cent to sporotricin, and none to coccidioidin.—*Primeiras pesquisas sobre a sensibilidade cutânea á histoplasmina no Estado do Rio Grande do Sul. Suas relações com as lesões pulmonares residuais, N. Marsiaj, A. Py, & N. Pêgas, Rev. brazil. med., March, 1950, 7: 157.*—(*A. A. Moll*)

Pulmonary "Coin" Lesion.—The solitary round, circumscribed, coin-like pulmonary lesion frequently is observed in asymptomatic persons as a result of mass roentgenography. Problems of diagnosis and management are inevitably raised. Where a final pathologic diagnosis is not possible after all available diagnostic measures have been exhausted, several procedures are available. One may watch the lesion by serial roentgenograms, give a "test-dose" of radiotherapy, or institute surgical exploration with removal of the lesion. Those who advocate watchful waiting must assume the risk that the lesion may progress unfavorably. A "test-dose" of radiotherapy will determine the radiosensitivity of the lesion but will not provide clear-cut evidence of the histology. There is a growing school of clinicians and surgeons who advocate prompt removal of these obscure peripheral lesions, 15 to 30 per cent of which are potentially malignant. This view is supported by the low operative mortality, by the positive diagnosis thus afforded, and by the high rate of curability. The age of the patient, the history, symptomatology, and physical findings play a part in all decisions regarding diagnosis and therapy. Of utmost importance are the size and shape of the lesion, its location, and the presence or absence of calcification and secondary lung changes. In those cases where a diagnosis of an innocuous lesion cannot be reasonably established, one must take into account the low mortality of present-day chest surgery, the accuracy of the histologic diagnosis, and the possibility of complete removal of an early malignant growth.—*The pulmonary "coin" lesion (editorial), Radiology, January, 1950, 54: 116.*—(*S. J. Steininger*)

Disability in Anthrosilicosis.—Disabling anthrosilicosis has long been recognized but criteria for evaluating the disability have been

inadequate. Pulmonary function tests now available should give a more accurate evaluation when combined with clinical, roentgenologic, and laboratory procedures. In 1948 and 1949 an unselected group of 375 hard coal miners with various states of silicosis were hospitalized for study; more than 150 had complete pulmonary function tests performed. The average age was 55 years, 42 per cent being from 51 to 60 years old. Underground exposure varied from 3 to 64 years, the average being 32 years. Of the 375 men only 47 (17 per cent) were still working, usually out of the mines; the remainder had stopped work for periods as long as 17 years, with an average period of work stoppage of 2.4 years. A history of respiratory infections was given by 76.4 per cent of the patients. Approximately three-fourths of the men stopped work because of dyspnea, which usually had a gradual onset extending over a period up to 18 years, the average being only 2 years, however. Hemoptysis was experienced by 35.8 per cent of the men but was given as the primary reason for stopping work by only 2.3 per cent. Approximately half of the men showed poor nutrition, 30 per cent were orthopneic, 73 per cent were emphysematous, and rales were present in 45 per cent. Tubercle bacilli were found in 44 cases (11.7 per cent), a positive Mantoux reaction in 89.5 per cent, significantly abnormal urinary findings were present in 32.7 per cent, and low fasting blood sugar (below 80 mg. per cent) in more than 60 per cent. Electrocardiographic evidence of right heart strain was found in 24 of the 148 patients tested. Of 108 roentgenologically asymmetrical lesions only 40 were proved tuberculous but of 37 cavitary lesions 30 produced tubercle bacilli. Associated medical conditions were considered sufficient, either individually or in combination, to produce disability in 186 cases regardless of the degree of impairment due to the silicosis itself. Complete pulmonary function studies in 150 cases, including ventilation measurement, evaluation of the degree of emphysema, and the respiratory gas exchange at rest and during exercise, showed that disability was due to changes in these factors in 50.5 per cent. Emphysema is regarded as the chief cause of disability.—*Studies in the clinical evaluation of disability in anthrosilicosis, P. A. Theodos, B. Gordon, L. P. Long, & H. L. Motley, Dis. of Chest, March, 1950, 17: 249.*—(*E. A. Rouff*)

Silicosis.—In order properly to evaluate the possibility of silicosis in a patient, 4 questions must be considered: (*1*) Does the patient have silicosis? (*2*) Did it occur in the course of his occupation? (*3*) What is the extent of his disability? (*4*) What is the prognosis? As a measure of the extent of disability, properly performed vital capacity and exercise tolerance tests are essential. Prognosis is difficult since some cases have been seen not to progress at all, while others reach maximum difficulty in six to twelve months. The presence of tuberculosis and of cardiac disease influence the prognosis.—*Medico-legal aspects of silicosis, M. H. Black, Tuberculology, August, 1948, 10: 10.* —(*L. Levin*)

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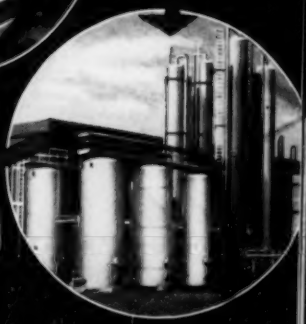

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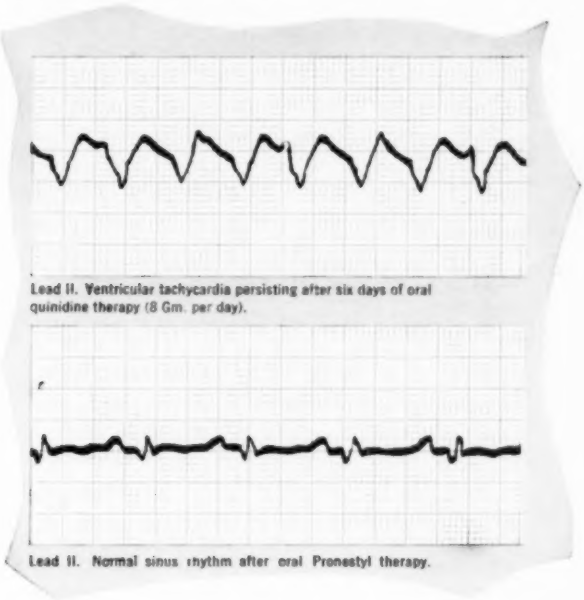

Lead II. Ventricular tachycardia persisting after six days of oral quinidine therapy (8 Gm. per day).

Lead II. Normal sinus rhythm after oral Pronestyl therapy.

Oral administration of Pronestyl in doses of 3-6 grams per day, for periods of time varying from 2 days to 3 months, produced no toxic effects as evidenced by studies of blood count, urine, liver function, blood pressure, and electrocardiogram. Pronestyl may be given intravenously with relative safety.

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Pronestyl Hydrochloride Capsules, 0.25 Gm., bottles of 100 and 1000.
Pronestyl Hydrochloride Solution, 100 mg. per cc., 10 cc. vials.

For detailed information on dosage and administration, write for literature or ask your Squibb Professional Service Representative.

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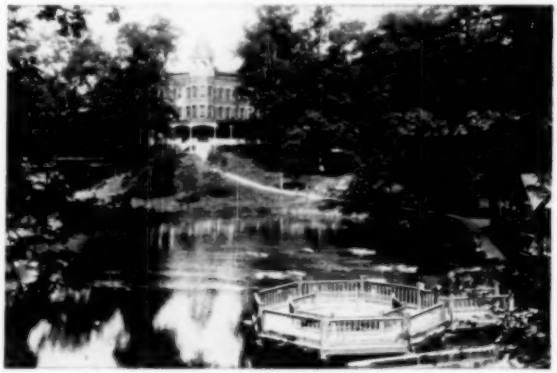

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1. King, E. Q.; Lewis, C. N.; Welch, H.; Clark, E. A., Jr.; Johnson, J. B.; Lyons, J. B.; Scott, R.B., and Cornely, P. B.: J. A. M. A. 143:1 (May 6) 1950.
2. Herrell, W. E.; Heilman, F. E.; Wellman, W. E., and Bartholomew, L. A.: Proc. Staff Meet. Mayo Clin. 25:183 (Apr. 12) 1950
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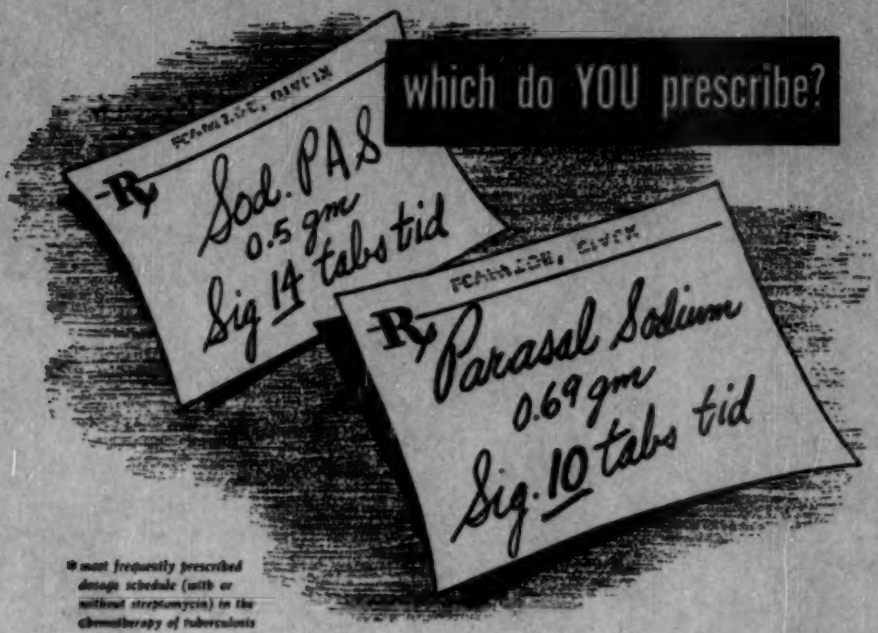

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